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RETROPERITONEAL TERATOMAS IN INFANCY AND CHILDHOOD

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RETROPERITONEAL tumors form an important group of neoplasms in infancy and childhood. The two most common retroperitoneal tumors in this age group are neuroblastoma sympatheticum and embryoma of the kidney (Wilms' tumor); teratomas are third in order of frequency. Thirty-nine cases (one by the author) of retroperitoneal teratoid tumors in infancy and childhood, established by the pathologic examination of surgical or necropsy specimens, have been recorded in the literature (table 1). In addition to these cases, three were observed in the Children's Hospital, Boston,[38] and two have been treated by the author.

DEFINITION AND HISTOGENESIS OF TERATOMAS

A teratoma is a tumor of multiple tissues of kinds foreign to the part in which it arises; it displays some degree of progressive uncoordinated growth and is not merely a quiescent malformation.[39]

Many speculative hypotheses as to the nature of teratomas have been advanced. From his careful review of the structure and behavior of these growths, Askanazy[40] concluded that they must arise from abnormal tissue primordia in early embryonic life which undergo chaotic differentiation into a variety of tissues. Budde[17] interpreted teratomas originating as the result of disturbances of the primitive streak since, with few exceptions, teratomas arise in an immediately preaxial median or paramedian position from the base of the skull to the coccyx. All the members of the extraperitoneal intra-abdominal group center about the vicinity of the primitive mesentery. The older theories that teratomas were distorted fetuses included within the host have been disproved by Willis[28] who found that teratomas show no signs of the possession of a vertebrate axis, or of delamination of germ layers, or of regional distribution of organs.

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TABLE 1

CASES OF RETROPERITONEAL TERATOMA IN INFANCY AND CHILDHOOD REPORTED IN LITERATURE

Author yr.	Age Sex	Clinical Manifestations	Tumor Location Size Consistency Germ Layer Derivatives	Operation Result
Dickinson,[1] 1871	2 yr. F	Abdominal mass since age of 3 mo.; anorexia and fever (late)	Left half of abdomen. 10×10×15 cm. Cystic and solid. Ectoderm and mesoderm.	None Necropsy
Hosmer,[2] 1880	8 mo. F	Abdominal enlargement since age of 1 mo.; anorexia, fever, and wt. loss (late); abdominal mass; dilated veins of abdominal wall.	Right half of abdomen. Child's head. Cystic and solid. Ectoderm, entoderm and mesoderm	None Necropsy
Bardenheurer,[3] 1887	17 yr. F	Abdominal mass for 1 yr.	Right side of abdomen. Child's head. Cystic and solid.	Incision of cyst (transperitoneal). Death 1 yr. after operation.
Gude,[4] 1898	9 yr. M	Abdominal mass	L.L.Q. of abdomen. 20×7 cm. Cystic and solid. Ectoderm and mesoderm.	Partial excision and marsupialization (transperitoneal). Death 9 days after operation.
Lexer,[5] 1900	11 yr. F	Abdominal mass, nausea, vomiting, and fever for 3 yr.	Both sides of abdomen. Cystic and solid. Ectoderm, entoderm and mesoderm.	Incision of cyst (extraperitoneal) Fistula for 3 yr. Excision (transperitoneal). Recovery; no follow-up.
Kon,[6] 1904	9 mo. M	Abdominal mass	Left half of abdomen. Child's head. Ectoderm, entoderm and mesoderm.	Excision Death
Schonholzer,[7] 1906	2 yr. M	Abdominal mass	L.U.Q. of abdomen. 12×10×11 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	None Necropsy
Durante and David,[8] 1907	Newborn		Both sides of abdomen. Fetal head. Ectoderm and mesoderm.	None Necropsy
Johnson and Lawrence,[9] 1909	3 yr. M	Abdominal mass for 3 mo.; scoliosis of lumbar spine	Left half of abdomen. 10×10×7.5 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Incision of cyst (extraperitoneal). Death
Kolb,[10] 1909	7 wk. F	Abdominal mass since age of 9 days; dilated veins of abdominal wall	Left half of abdomen. 12×15×7.5 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	None Necropsy
Kusnetzow,[11] 1910	4 mo. M	Abdominal mass	Left half of abdomen. 7 mo. pregnant uterus. Entoderm and mesoderm.	None Necropsy
Bauer,[12] 1911	14 yr. M	Abdominal enlargement for 5 mo.; abdominal pain and loss of wt.; abdominal mass; dilated veins of abdominal wall	Left half of abdomen. Child's head. Cystic and solid. Ectoderm and mesoderm.	Incision of cyst (extraperitoneal). Death 23 days after operation.
Sand and Lerat,[13] 1912	15 yr. M	Abdominal mass for 10 yr.; fever for 2 wk.	L.U.Q. of abdomen. Large. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (extraperitoneal). Death 9 wk. after operation.
Portugal,[14] 1919	17 yr. F	Abdominal mass for 9 yr.; abdominal pain and vomiting for 8 yr.	L.U.Q. of abdomen. 12×7 cm. Cystic and solid. Ectoderm and mesoderm.	Incision and marsupialization of cyst (transperitoneal). Death 4 days after operation.

TABLE 1—(*continued*)

Author yr.	Age Sex	Clinical Manifestations	Tumor Location Size Consistency Germ Layer Derivatives	Operation Result
Tsuda,[15] 1920	17 mo. M	Abdominal mass	Left half of abdomen. Man's head. Ectoderm, entoderm and mesoderm.	Excision. Death 12 hr. after operation.
Kaneko,[16] 1924	10 mo. M	Abdominal distension since age of 4 mo.; abdominal mass	Both sides of abdomen. Man's head. Ectoderm, entoderm and mesoderm.	None Necropsy
Budde,[17] 1926	2 mo. M	Abdominal enlargement and vomiting since age of 3 days; abdominal mass; dilated veins of abdominal wall	Both sides of abdomen. Two fists. Cystic and solid. Ectoderm, entoderm and mesoderm.	Incision (transperitoneal). Death 4 days after operation.
Seki,[18] 1927	22 mo. M	Abdominal mass	Left half of abdomen. Infant's head. Cystic and solid. Ectoderm, entoderm and mesoderm.	None Necropsy
Nicholson,[19] 1929	4 mo. F		L.U.Q. of abdomen. 11.5×8.5×5 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	None Necropsy
Paltauf,[20] 1931	5 mo. F	Abdominal mass	Left half of abdomen. Fist. Cystic and solid. Ectoderm, entoderm and mesoderm.	None Necropsy
Lightwood,[21] 1932	9 wk. F	Abdominal enlargement and constipation since birth; abdominal mass; RG: calcified areas; displacement of kidney downward in pyelogram	R.U.Q. of abdomen. Orange. Cystic and solid. Ectoderm and mesoderm.	Excision. Recovery; no follow-up.
Lundblad,[22] 1932	4 yr. F	Abdominal mass since birth	Left side of abdomen. Man's head. Cystic and solid. Ectoderm and mesoderm.	Excision (transperitoneal). Death day of operation.
Lundblad,[22] 1932	4 yr. F	Anorexia, abdominal pain, and vomiting for 3 mo.; abdominal mass for 1 wk.	Right side of abdomen. Goose egg. Cystic and solid. Entoderm and mesoderm.	Excision (extraperitoneal). Death 8 mo. after operation.
Froeboese,[23] 1932	15 mo. F	Abdominal mass since age of 3 mo.; loss of wt. (late)	R.U.Q. of abdomen. Ostrich egg. Cystic and solid. Ectoderm, entoderm and mesoderm.	None Necropsy
Weier,[24] 1932	18 mo.	Abdominal enlargement for 5 mo.; abdominal mass	Both sides of abdomen. Large. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (transperitoneal). Recovery; well 5 mo. after operation.
Campbell,[25] 1933	6 mo. M	Abdominal mass for 1 day; RG: calcified areas; displacement of kidney laterally in pyelogram	Both sides of abdomen. 11.5×12 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (extraperitoneal). Recovery; well 18 mo. after operation.
Watanabe,[26] 1933	23 mo. M	Abdominal mass	Left side of abdomen. 14×10.3×9.5 cm. Ectoderm and mesoderm.	None Necropsy
Terasako,[27] 1934	3 mo. M	Abdominal mass	Right side of abdomen. 15×9×8 cm. Ectoderm and mesoderm.	None Necropsy

TABLE 1—(*continued*)

Author yr.	Age Sex	Clinical Manifestations	Tumor Location Size Consistency Germ Layer Derivatives	Operation Result
Willis,[28] 1935	9 wk. F	Abdominal enlargement since birth; abdominal mass	Right side of abdomen. 8 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision. Recovery; no follow-up.
Willis,[28] 1935	9 mo. F		Right side of abdomen. 16×10 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision. Recovery; no follow-up.
Nicholson,[29] 1935	7 mo. F	Abdominal enlargement for 5 mo.; abdominal mass	Both sides of abdomen. 17×15×9 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (transperitoneal). Recovery; well 5 yr. after operation.
Eerland,[30] 1938	8 mo. F	Abdominal mass since age of 6 wk.	Both sides of abdomen. Large. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (extraperitoneal). Recovery; well 3 mo. after operation.
Arnheim,[31] 1943	3 mo. F	Abdominal enlargement and constipation for 6 wk.; abdominal mass; dilated veins of abdominal wall; RG: calcified areas; displacement of intestines	Both sides of abdomen. 20 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (transperitoneal). Recovery; well 8 yr. after operation.
Gale and Willis,[32] 1944	13 yr. F	Abdominal mass	Midline of abdomen. 9.5×6.5×5 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Partial excision (transperitoneal). Recovery; well 16 mo. after operation.
Smith and Cochrane,[33] 1946	2 mo. M	Abdominal mass for 6 wk.; RG: calcified areas; displacement of kidney in pyelogram	Left side of abdomen. Cystic and solid. Ectoderm, entoderm and mesoderm.	Partial excision and marsupialization (extraperitoneal). Recovery; well 4 yr. after operation.
O'Leary and Halpert,[34] 1947	15 mo. F	Abdominal enlargement for 9 mo.; abdominal mass; RG: displacement of kidney downward in pyelogram.	Both sides of abdomen. 37×28×9 cm. Cystic and solid. Ectoderm and mesoderm.	Excision (transperitoneal). Recovery; well 2 yr. after operation.
Langley,[35] 1950	9 yr. M	Abdominal mass for 1 wk.; RG: calcified areas; displacement of kidney posteriorly in pyelogram	Right side of abdomen. 17.5×12.5×10 cm. Cystic and solid. Ectoderm and mesoderm.	Excision (transperitoneal). Recovery; well 16 mo. after operation.
Baker and Ragins,[36] 1950	10 yr. F	Abdominal pain and fever for 10 yr.; dysuria and frequency of urination for 2 yr.; abdominal mass; RG: calcified areas; displacement of kidney posteriorly in pyelogram	L.U.Q. of abdomen. 8×4.5×5.5 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (extraperitoneal). Recovery; well 1 mo. after operation.
Cohen, Marcus and Sherwin,[37] 1950	3 mo. F	Abdominal enlargement for 1 mo.; abdominal mass; RG: calcified areas	Both sides of abdomen. 13×10×11 cm. Cystic and solid. Ectoderm, entoderm and mesoderm.	Excision (transperitoneal). Recovery; well 1 yr. after operation.

Structure of Teratomas[39]

Teratoid tumors contain representatives of the embryonal elements—ectoderm, entoderm and mesoderm—with no evidence of orderly delamination. Almost all teratomas are tridermal, for they almost all contain skin, teeth or nervous tissue (ectoderm), res-

piratory or alimentary epithelia (entoderm), and they all contain connective and vascular tissue at least (mesoderm). The component tissues are adult or embryonic, mature or immature. The most benign teratomas consist of fully mature tissues with no sign of proliferative activity; the most malignant ones contain abundant immature embryonic tissues. A malignant tumor may arise from one of the previously quiescent tissues of the growth or may be a property of the whole growth, shared by all its immature tissues though not necessarily in equal degrees. Teratomas may be predominantly cystic growths or predominantly solid growths, but both types of tissues are represented; the cysts are usually multiple, with one large cyst occupying the greater part of the tumor.

Pathologic Features of Retroperitoneal Teratomas

Retroperitoneal teratomas are usually large cystic tumors which arise high in the retroperitoneal space, close to the pancreas and kidneys, and may occupy the complete retroperitoneal space on one side or extend into both sides of the retroperitoneal space.

Nineteen tumors were located on the left side of the abdomen, 11 on the right side and 14 on both sides; the bilateral tumors occupied more of one side of the abdomen, and extended beyond the midline to the opposite side.

Large retroperitoneal teratomas cause death by pressure effects; 13 tumors (29.5%) were not operated upon and were described at autopsy. Malignant changes were noted in three cases (6.8%). The low incidence of malignancy results in few instances of metastases. Since a malignant tumor may arise from one of the previously quiescent tissues of the growth, and since 52.2% of retroperitoneal teratomas were seen in the first year of life, it is probable that the incidence of malignancy would be greater if observation had occurred later in life.

Clinical Features of Retroperitoneal Teratomas

The ages of the patients were as follows:

Cases	Age
23 (52.2%)	0 to 1 yr.
6	1 to 2 yr.
5	2 to 5 yr.
3	5 to 10 yr.
4	10 to 15 yr.
3	15 to 20 yr.

Both sexes were represented: 26 females, 16 males and 2 not recorded.

Abdominal enlargment and a palpable mass were the most common findings. Symptoms were predominantly the result of pressure incident to the size of the tumor. Many of the masses had not increased in size during observation for several months. Abdominal pain was an infrequent symptom; the early age of the patients was probably a factor. Later in the course of observation, fever, vomiting, loss of weight, anorexia and constipation were occasionally noted. Although such tumors were in close proximity to the kidneys, urinary symptoms have only been observed in one case. The masses were usually large and firm in consistency, of limited mobility, and ballotable into the lumbar region. Dilated veins of the abdominal wall were occasionally noted.

Roentgen studies were performed in 12 cases, revealing areas of ossification in the tumor. In 9 cases intravenous or retrograde pyelography showed kidney or ureter displacement.

Diagnosis of Retroperitoneal Tumors

As previously stated, the two most common retroperitoneal tumors in infancy and childhood are neuroblastoma sympatheticum and embryoma of the kidney (Wilms' tumor). These neoplasms are most frequently found in children between the ages of 2 and 4 years, although infants and older children have been affected. Symptoms of weight loss, anorexia and fatigue are more common in neuroblastomas. Although urinary symptoms are uncommon in all these tumors, the presence of hematuria would suggest a diagnosis of Wilms' tumor. The masses in neuroblastomas are usually nodular with poorly defined borders. The masses in Wilms' tumors more closely resemble those of teratomas, but are more commonly smaller in size and confined to one side of the abdomen. Plain roentgen films of the abdomen usually reveal the shadow of the tumor and often displacement of intestinal loops. Areas of ossification are noted in both teratomas and neuroblastomas. Excretory or retrograde pyelography is more likely to show distortion of the renal pelvis and calyces in Wilms' tumor. Roentgen studies of the chest, skull, long bones, spine, and pelvis should always be performed in cases of abdominal tumors in childhood because multiple destructive lesions of the skull and long bones are often found in neuroblastomas, whereas metastases limited to the lungs are more characteristic of embryoma of the kidney.

Treatment and Results

The treatment of retroperitoneal teratomas is operative removal. A transperitoneal, transverse, liberal incision is the best approach for the excision of these tumors. The necessity for the removal of such tumors is evidenced by the death of the 13 untreated children. The operative mortality has been high, 9 of the 31 operations (29%); the causes of death were incomplete removal, hemorrhage and shock. Twenty operative recoveries were reported in the past two decades, and these patients had the benefits of intravenous infusions or transfusions.

Of the 19 children discharged from the hospital after removal of benign retroperitoneal teratomas, 4 had no follow-up observations, and 2 died within the first year after operation; 3 were well under 1 year, 6 from 1 to 2 years, and 1 each at 2, 4, 5 and 8 years after operation. The 3 children with malignant retroperitoneal teratomas survived operation, but 2 died of recurrences and metastases 4½ months and 7 months after operation; follow-up data were not available in the remaining case.

Case Reports

Case 1.* History: A white female infant, aged 3 mo., was admitted to the Mount Sinai Hospital because of enlargement of the abdomen and constipation since the age of 6 wk. Patient had been a full term, normal delivery with birth weight of 3,685 gm. Family history irrelevant.

Physical examination: On admission examination revealed a well developed and well nourished infant. Her temperature was 37.5°C. and she weighed 5,500 gm. There were no abnormalities of the head, heart, lungs, extremities or genitalia. Pea-sized lymph nodes were palpable in the cervical, axillary and inguinal regions.

Dilated veins in the abdominal wall were noted. There was marked swelling of the abdomen with an obvious bulge in the left flank (Fig. 1). This enlargement was produced by a huge mass which filled the left flank and the left side of the abdomen from the costal margin to the pelvis, with an extension of the mass into the right lower quadrant. The tumor was firm, elastic and ballotable into the left lumbar region. Several walnut-sized hard masses were palpable in the right lower quadrant

* Included in table 1.

of the abdomen separate from the large tumor. The edge of the right lobe of the liver was felt at the costal margin. The spleen was not palpable. On rectal examination, a hard nodule was felt high on the right side.

Laboratory Data: On admission the RBC was 5.9 million/cmm.; WBC 16.1 thousand/cmm. with 24% polymorphonuclear leukocytes, 64% lymphocytes, 6% myelocytes, 3% monocytes, 2% eosinophils, 1% basophils; Hgb. 15.8 gm./100 cc. Blood urea N was 21 mg./100 cc. A urinalysis was normal except for a faint trace of albumin. Wassermann, Schick, Mantoux and Brucella tests were negative.

FIG. 1. Case 1. Abdominal enlargement at 3 mo. of age, before operation.

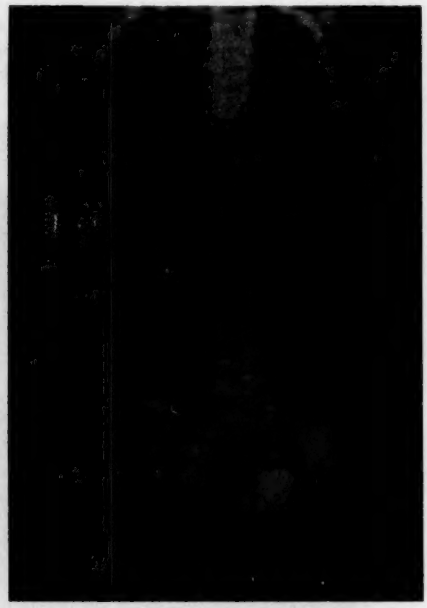

FIG. 2. RG of abdomen and excretory urogram on Case 1 preoperatively, showing large mass filling most of abdomen and displacing intestines to right side; areas of ossification in tumor are visualized just above right iliac crest; renal pelvis is outlined on right side and faintly seen on left.

Roentgenograms: RGs of the chest and long bones were normal. RG of the abdomen showed a large mass filling the left side and part of the right side of the abdomen; small areas of irregular ossification were noted on the right side just above the iliac crest. Intravenous pyelography revealed the mass as noted in the RG of the abdomen, with the intestines displaced to the right side of the abdomen; no abnormality was noted in the right upper urinary tract; the left kidney pelvis was only faintly visualized, but no gross abnormality in the contour of the calyces was demonstrated (Fig. 2).

Operation: Operation was performed 2 days after admission. Under ether anesthesia, a long, oblique, transperitoneal incision was made.

A large tumor presented, filling most of the abdominal cavity. The tumor measured about 20 cm. in diameter, and was spherical in outline. The appearance and consistency of the tumor varied; much of it was cystic, its wall whitish in color and thick. In the lower solid portion of the tumor, areas of calcification were felt. The mass encroached upon the entire length of the descending colon which overlay its left lateral surface. The left colic vessels were in close proximity, and in places adherent, to the wall of the tumor. The small intestines and a mobile cecum were compressed into the right lumbar gutter.

In order to reduce the size of the cystic portion of the tumor, a trocar and cannula were inserted into it and about 600 cc. of white mucoid fluid were aspirated. A plane of cleavage was established to the left of the tumor and developed just mesial to the colic vessels. At the areas of close attachment to the vessels, where dissection was more difficult and where the wall of the tumor was thick,

FIG. 3. Operative specimen in Case 1 showing cystic and solid structure of tumor.

some bleeding was encountered from the branches of the left colic vessels. The third portion of the duodenum and the first loop of jejunum were adherent to the dome of the tumor, but these structures were separated from the mass without difficulty. The solid portion of the tumor, in its lower right half, was relatively fixed posteriorly, but could be satisfactorily mobilized. When complete mobilization of the tumor on all sides had been performed, no fixed attachment posteriorly was found. After removal of the tumor, most of the lumbar retroperitoneal space, the aorta, the inferior vena cava and the left kidney and ureter were exposed. There was no obvious bleeding from the retroperitoneal tissues. Two broad layers of the posterior peritoneum were then developed, extending from the ascending colon on the right to the descending colon on the left, from the third portion of the duodenum above to the iliac region below, and approximated. The abdominal wall was closed in layers.

Report of Pathology: The specimen was a cystic tumor which measured about 15 cm. in diameter (Fig. 3). The surface was nodular, in part smooth, and in part covered by membranous adhesions. Most of the surface was white in color, but there were some bluish nodules and areas of hemorrhage. The cystic portion of the tumor was made up of a large cyst and many smaller cysts; several daughter-cysts were found in the wall of the large cyst. One portion of the wall of the large cyst consisted of

nerve tissue and cartilage. Bone was found in one of the daughter-cysts. The smaller solid portion of the tumor, in the bluish nodules, was made up of cartilage and nerve tissue.

On microscopic examination, representatives of the 3 embryonal layers were found (Fig. 4A and 4B). The mesodermal elements predominated as cartilage, bone, smooth muscle, fat and connective tissue. The structures of ectodermal origin were squamous epithelium which lined many of the cysts, sebaceous glands and nerve tissue. Entodermal tissues were least frequent and were represented by columnar epithelium and goblet cells as seen in the large intestines, and columnar ciliated epithelium suggesting bronchial mucous membrane.

Course: An intravenous infusion of 5% dextrose in saline and citrated blood were given during the operation. Additional transfusions of citrated blood were administered on the first and second postoperative days. During this period the intravenous dextrose saline was continued. During the

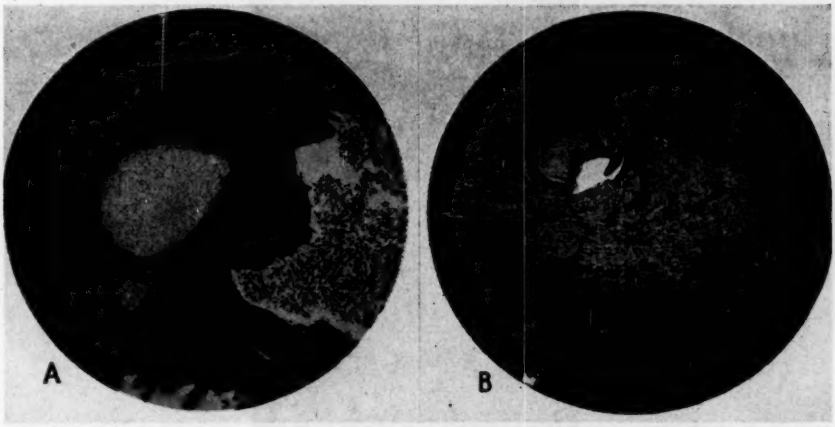

FIG. 4 A. Microscopic sections of tumor in Case 1 showing cartilage, smooth muscle and cystic area lined by squamous epithelium (×45). B. Island of squamous cells surrounded by cerebral tissue (×30).

second and third postoperative days 2 gm. of sulfathiazole were given. Feedings were started on the second day.

There were rises in temperature to 40°C. on the first postoperative day, 39.4°C. on the second day, and 38.5°C. on the seventh day; the temperature was otherwise normal. Convalescence was uneventful after a period of slight shock during the 1st 48 hr. after operation. The dermal sutures were removed 1 wk. after operation. The wound healed by primary union except for a small area of superficial subcutaneous infection. The infant was discharged 17 days after operation in good condition and weighing 4,366 gm.

Follow-up examinations were carried out over a period of 8½ yr.; during this period the child progressed well and steadily gained weight. RG of the abdomen, at the age of 8 yr., revealed no abnormalities. At the time of the last examination, when the patient was 8½ yr. of age, the weight was 34 kg., and the height was 133 cm. The abdomen was of normal contour presenting a firmly healed oblique wound in the left upper quadrant (Fig. 5).

Case 2. History: A white female infant, aged 6 mo., was admitted to the Beth-El Hospital because of enlargement of the abdomen for 1 mo. Patient had been a full term, normal delivery with birth weight of 2,835 gm.

The mother and father were living and well. The maternal grandmother had died of cancer. There were no siblings.

Physical Examination: On admission, examination revealed a well developed and well nourished infant. Her temperature was 37.2°C., and she weighed 6,464 gm. There were no abnormalities of the head, heart, lungs, extremities or genitalia.

The superficial abdominal veins were more prominent on the right side. The abdomen was markedly enlarged, fairly symmetric in outline, but showing more fullness on the right. A large mass filled the right flank and the right side of the abdomen, and extended across the midline into the left side of the abdomen for a distance of about 8 cm. The tumor was smooth, firm, slightly movable, and

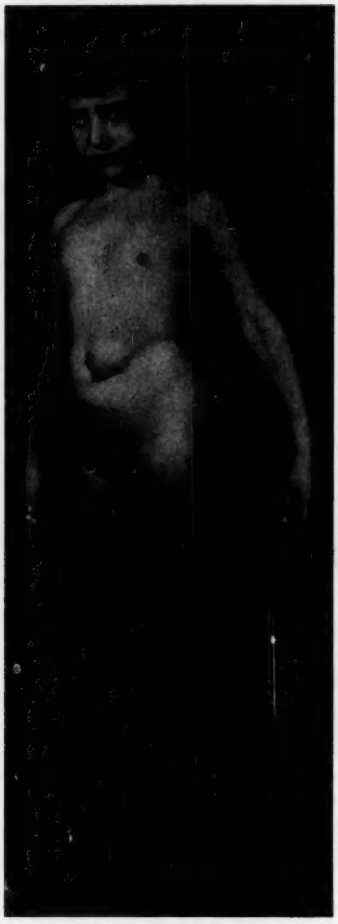

FIG. 5. Case 1 at 8½ yr. of age, showing good nutrition and operative scar.

ballotable into the right lumbar region. The liver and spleen were not palpable. Rectal examination was negative.

Laboratory Data: On admission the RBC was 3.8 million/cmm.; WBC 7 thousand/cmm. with 50% polymorphonuclear leukocytes and 50% lymphocytes; Hgb. 10.8 gm./100 cc. Urine contained occasional WBC and RBC. Blood urea N was 14.2 mg./100 cc.; total protein 6.1 gm./100 cc.; albumin 3.6 gm./100 cc.; globulin 2.5 gm./100 cc.; sugar 84 mg./100 cc.; alkaline phosphatase 5.2 Bodansky u.

Roentgenograms: RGs of the chest, skull and long bones were normal. RGs of the abdomen showed a large mass filling the right side and part of the left side of the abdomen, extending from the abdominal wall to the vertebral column, and displacing the intestines to the left side of the abdomen

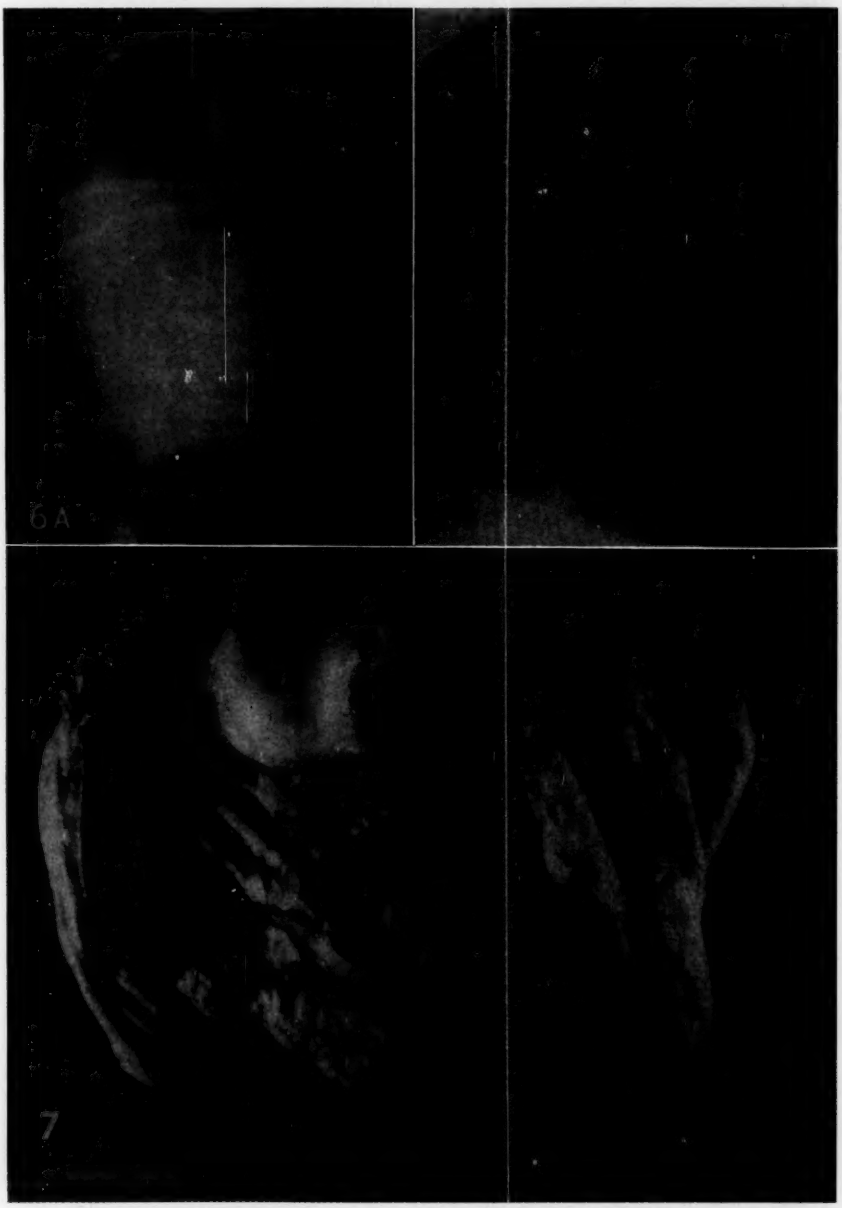

FIG. 6. A. RGs of abdomen on Case 2 preoperatively, showing large mass filling most of abdomen and displacing intestines to left side. B. Lateral view showing mass extending from abdominal wall to vertebral column.

FIG. 7. Operative specimen in Case 2 showing interior of cyst wall.

(Fig. 6A and 6B). Intravenous pyelography revealed moderate distention of the renal pelvis of the right side as compared to the left side.

Operation: Operation was performed 1 day after admission. Under ether anesthesia, a long, transverse, transperitoneal incision was made.

A large, round, white, cystic tumor presented, filling the right side and a portion of the left side of the abdomen, extending from the under surface of the liver downward into the pelvis. The cyst measured about 12 cm. in diameter; its wall was thin and closely attached to the posterior peritoneum, mesosigmoid, and broad ligament, resulting in adhesions of the sigmoid and right Fallopian tube and ovary to it. Loops of small intestine were displaced far into the left side of the abdomen, and

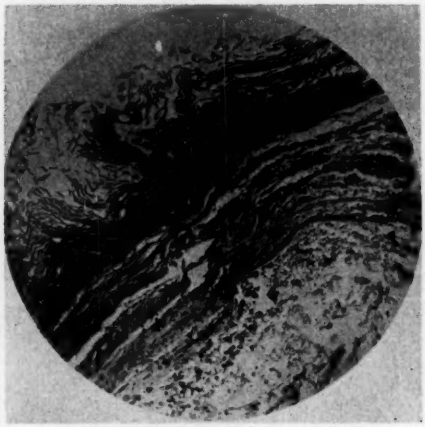

FIG. 8. Microscopic section of tumor in Case 2 showing smooth muscle lined by squamous epithelium (×45).

the transverse colon was displaced upward. The cyst arose from the right retroperitoneal space, closely attached to the anterior surface of the right half of a horseshoe kidney. A dilated structure was felt within the renal tissue at the juncture of the cyst and kidney, which probably represented a dilated renal pelvis. The right side of the horseshoe kidney appeared larger than the left side; the transverse segment over the vertebral column was quite thick, measuring about 3 cm. in diameter. The ureters were not visualized. Two thick, yellow plaques of tissue, about 2 cm. in diameter, were found in the wall of the cyst near the renal attachment.

The closely attached posterior peritoneum, mesosigmoid, and broad ligament were dissected from the wall of the cyst. The attachment of the cyst to the horseshoe kidney was exposed, divided between clamps, closed with fine silk sutures, and the tumor was removed. The posterior peritoneum was closed with interrupted sutures of fine silk. The abdominal wall was closed in layers.

Report of Pathology: The specimen was a smooth-walled cyst which measured 12 cm. in diameter (Fig. 7). At one end of the cyst there were 2 raised areas, each measuring about 3 cm. in diameter. The lining of the cyst showed a deposition of white tissue resembling stratified squamous epithelium. On section the tumor was filled with a cloudy, yellow fluid containing small pieces of white and yellow material.

On microscopic examination, the cyst wall was composed of smooth muscle lined by squamous epithelium (Fig. 8).

Course: An intravenous infusion of 5% dextrose in saline and citrated blood was administered during the day of operation. The infant was kept in a cubicle through which oxygen was supplied. An indwelling Levin tube was inserted into the stomach. Penicillin, 300,000 u. daily by intramuscular injection, was started.

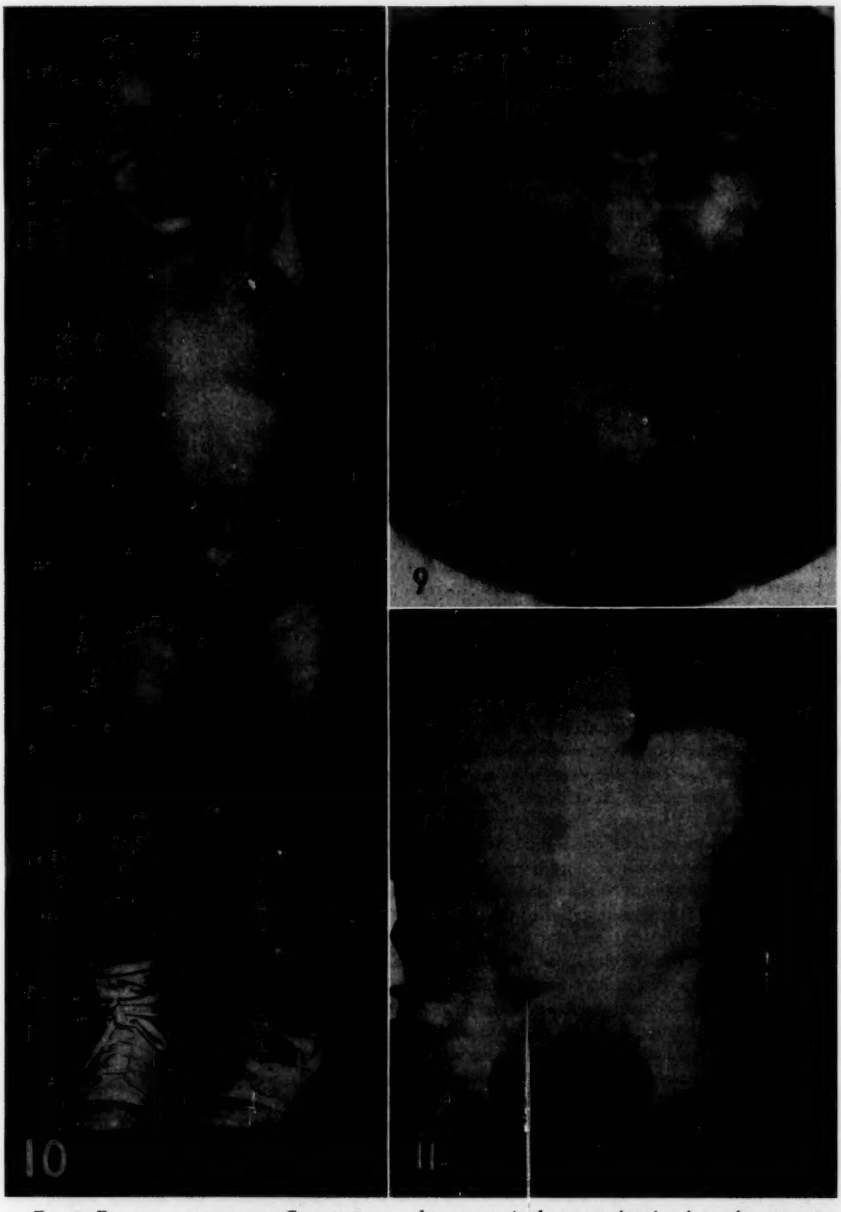

FIG. 9. Excretory urogram on Case 2, 2 mo. after removal of tumor, showing horseshoe contour, and rotation of pelvis, of left kidney, mass on right side of abdomen, and no visualization of right renal pelvis.

FIG. 10. Case 2, at 20 mo. of age, showing good nutrition and operative scars.

FIG. 11. RG of abdomen on Case 3 preoperatively, showing large mass filling most of abdomen, displacing stomach upward and intestines downward.

During the first postoperative day feedings of dextrose water were retained. The infant's good condition was maintained by the therapeutic measures started on the day of operation. The abdomen was soft and not distended. The urinary output was adequate. The highest temperature was 38.8°C. RBC was 4.8 million/cmm.; WBC 8.4 thousand/cmm. with 40% polymorphonuclear leukocytes, 58% lymphocytes and 2% monocytes; Hgb. 16.5 gm./100 cc. Urine contained occasional WBC.

The intravenous infusion, gastric siphonage and oxygen therapy were discontinued on the second postoperative day. The highest temperature was 38.4°C. During the remainder of the first postoperative week the infant's condition remained good, she ate well and the temperatures were normal. The urinary output was adequate. There were 1 to 3 normal bowel movements daily. Penicillin was discontinued on the sixth day, a total of 2,100,000 u. The wound healed by primary union, and the skin sutures were removed on the seventh day. At the end of the first week RBC was 4.4 million/cmm. and Hgb. 16.0 gm./100 cc. Urine contained occasional WBC. The patient was discharged on the fourteenth postoperative day, weighing 6,024 gm.

Follow-up examination, 1 mo. after operation, revealed a firm mass, measuring about 5 x 3 cm. in diameter, in the right paraumibilical region of the abdomen. The wound was firmly healed. The infant progressed well and there were no symptoms. Examination, 2 mo. after operation, showed increase in the size of the abdominal mass.

The infant, aged 8 mo., was readmitted to the hospital. She was well developed and well nourished, and she weighed 7,115 gm. A large firm mass filled most of the right side of the abdomen and extended into the right flank. The abdominal wound was healed.

RBC was 4 million/cmm.; WBC 11.8 thousand/cmm. with 62% polymorphonuclear leukocytes, 32% lymphocytes, 5% monocytes and 1% eosinophils; Hgb. 12.9 gm./100 cc. Urine contained 10 to 15 WBC/hpf. Blood urea N was 14.2 mg./100 cc.; total protein 7.5 gm./100 cc.; albumin 4.5 gm./100 cc.; globulin 3 gm./100 cc.; calcium 10.2 mg./100 cc.; chlorides 101 mEq./l.; alkaline phosphatase 4.2 Bodansky u.; phosphorus 3.8 mg./100 cc.; carbon dioxide content 19.8 mEq./l.

Intravenous pyelography revealed the horseshoe contour of the renal mass on the left side, and a large opacity on the right side obscuring the renal shadow; the left pelvis was well visualized and somewhat rotated, and there was no excretion of the dye on the right side (Fig. 9).

Operation: Under ether anesthesia, a right rectus muscle-splitting incision was made.

A large, round, cystic mass presented, filling most of the right side of the abdomen, and extending from the under surface of the liver downward into the lower abdomen. The cyst measured about 10 cm. in diameter; its wall was bluish in color and thick. The mesenteries of the ascending, transverse and sigmoid colon were adherent to the mass. Loops of small intestine were displaced into the left lower part of the abdomen. The first and second parts of the duodenum were adherent to the lateral wall of the cyst. The mass arose from the right retroperitoneal space, the site of origin being the anterior wall of the right half of a horseshoe kidney in the location of the pelvis. The right renal vessels entered the upper pole of that half of the kidney. The isthmus of the kidney was about 2 cm. in diameter. The right adrenal gland appeared normal.

The closely attached mesenteries of the colon were dissected from the wall of the cystic mass. The major portion of the cyst and its fluid contents were removed. It was then established that the mass was a large hydronephrosis of the pelvis of the right half of a horseshoe kidney; the openings of the calyces presented in its posterior wall. A right heminephrectomy was performed. The posterior peritoneum was closed over the renal stump. The abdomen was closed.

Report of Pathology: The specimen was a kidney and cystic mass of tissue. The kidney measured 5 x 4 x 2 cm. in diameter; its surface presented fetal lobulations. The pelvis was markedly dilated and focally hemorrhagic. The cystic mass measured 12 cm. in its opened state; its inner surface was coarsely trabeculated.

After microscopic examination, a diagnosis of obstructive hydronephrosis with chronic active pyelonephritis was made.

Course: The infant's postoperative course was uncomplicated, using the same therapeutic measures employed after the first operation. The wound healed by primary union. The urinary output was adequate. On the twelfth day the blood urea N was 13.5 mg./100 cc. and the total protein 7.7 gm./100 cc. Urine contained 1 to 2 WBC/hpf. The infant was discharged on the fourteenth postoperative day, weighing 6,662 gm.

Follow-up examinations were carried out over a period of 1 yr., during which period the child progressed well. At the time of the last examination, when she was 20 mo. of age, weight was

10 kg. and height was 79 cm. Urine contained 1 to 2 WBC/hpf. The abdomen was of normal contour presenting firmly healed transverse and vertical wounds (Fig. 10).

Comment: There is no report in the literature of a retroperitoneal teratoma attached to a horseshoe kidney. A dilated renal pelvis of the right half of the horseshoe kidney was present at the time of removal of the teratoma, and rapidly progressed to a large hydronephrotic sac.

Case 3. History: A white female child, aged 6 yr., was admitted to the Mount Sinai Hospital because of an abdominal mass noted by a physician 2 wk. before.

The child had pertussis at the age of 1 yr. Severe attacks of asthma accompanied by coughing occurred at intervals of 3 to 4 wk. since the age of 2 yr.; the abdominal mass was noted during examination in one of these episodes. The child had fallen from a swing, striking the abdomen, 6 mo. prior to admission to the hospital; since that time she complained of some pain in the left upper quadrant of the abdomen during paroxysms of severe cough. An hemangioma of the right leg had been excised at the age of 4 mo.

The mother and father were living and well. There was one sibling.

Physical Examination: On admission examination revealed a well developed child in moderate respiratory distress. Temperature was 37.5° C., pulse rate 136/min., and respiratory rate 24/min. She weighed 19.5 kg. Examination of the chest showed poor expansion, hyperresonant percussion note, prolongation of expiratory phase of respiration, diminished breath sounds and inspiratory and expiratory wheezes and rhonchi. There were no abnormalities of the head, neck, heart, extremities or genitalia.

The abdomen was enlarged, showing more fulness in the left side. A large mass filled the left side of the abdomen and left flank, and extended across the midline into the right side of the abdomen. The tumor was smooth, hard, slightly movable and ballotable into the left lumbar region. The liver and spleen were not palpable. Rectal examination was negative.

Laboratory Data: On admission the RBC was 3.5 million/cmm.; WBC 8.8 thousand/cmm. with 40% polymorphonuclear leukocytes, 46% lymphocytes, 5% monocytes, 7% eosinophils and 2% basophils; Hgb. 11 gm./100 cc. Urine contained 2+ albumin and 6 to 8 WBC.

Roentgenograms: RGs of the chest, skull, and long bones were normal. RG of the abdomen showed a homogeneous density filling the left side and part of the right side of the abdomen; the stomach was compressed and displaced upward and the intestines downward by the mass (Fig. 11). Intravenous pyelography revealed faint visualization of the renal pelvis on both sides.

Operation: Operation was performed 3 days after admission, when the status asthmaticus was under control. Under ether anesthesia, a long, transverse, transperitoneal incision was made.

There was a small amount of clear fluid in the peritoneal cavity. The entire operative field was filled with a large tumor, measuring about 15 cm. in diameter. The tumor was nodular and lobulated, the nodules varying considerably in size, shape and color; many were dark red, while others were pale white and tan, and some showed areas of hemorrhage visible on the surface. The tumor was retroperitoneal, covered by a thin layer of the posterior peritoneum; it displaced the transverse colon upwards, the descending colon laterally, and the loops of small intestine into the lower and right side of the abdomen. The liver was normal in appearance.

The posterior peritoneum was divided and the tumor carefully mobilized. In the course of mobilization it was found that the tumor was adherent to a segment of the tail of the pancreas, measuring about 5 cm. in length. The left kidney and adrenal were normal in appearance, and not adherent to the tumor. The lumbar vessels entering the tumor were divided and ligated. The tumor and adherent portion of the tail of the pancreas were removed. Vascular changes in the spleen were noted, due to the ligation of the splenic blood vessels in the course of the partial pancreatectomy; a splenectomy was performed. The entire left lumbar retroperitoneal space was exposed. No enlarged lymph nodes were found, but a few lymph nodes in the upper retroperitoneal space were removed for examination. The posterior peritoneum was closed about a Penrose drain. The abdomen was closed.

Report of Pathology: The specimens were a tumor which measured about 15 cm. in diameter and weighed about 350 gm., a segment of pancreas about 5 cm. in length and the spleen (Fig. 12). The surface of the tumor was nodular and partially covered by a smooth membrane. The nodules varied in color—white, tan and dark red; some areas of hemorrhage were seen. The tumor was soft and gelatinous in consistency, fragments of tissue being detached with ease. On section there was a varied appearance, corresponding to the changes in color of the nodules. The segment of the pancreas

on the posterior surface of the specimen appeared normal, did not seem to be infiltrated by the tumor, nor did the tumor appear to arise from the pancreatic parenchyma. The spleen weighed 60 gm. and appeared normal; the hilum was not infiltrated by the tumor. One of the small lymph nodes showed calcification.

On microscopic examination, the tumor was found to consist of immature, undifferentiated epithelial cells as in embryonal cell carcinoma (Fig. 13). Diagnosis: malignant teratoma. The segment of pancreas was infiltrated by the tumor. The spleen and 2 lymph nodes were not involved.

Course: An intravenous infusion of 5% dextrose in saline and water and citrated blood were

FIG. 12. Operative specimen in Case 3 showing nodular structure of tumor; spleen and segment of pancreas are attached.

administered during the day of operation. An indwelling Levin tube was inserted into the stomach. Penicillin 600,000 u. daily by intramuscular injection was started.

During the first postoperative day fluids were given by mouth and gastric siphonage was discontinued. During the next 3 days the condition remained good; the highest temperature was 38.6° C. The urinary output was adequate. RBC was 3.98 million/cmm.; WBC 17.2 thousand/cmm. with 86% polymorphonuclear leukocytes, 13% lymphocytes and 1% monocytes.

The intravenous infusion was discontinued on the fourth postoperative day. The temperature remained normal thereafter. The child was allowed out of bed on the fifth day. The wound healed by primary union and the skin sutures were removed on the seventh day. Penicillin was discontinued on the eighth day, a total of 4,200,000 u. The child was discharged on the tenth postoperative day. It is of interest that there was no respiratory difficulty during the postoperative course.

Follow-up examinations were made at monthly intervals for a period of 3 mo.; during this period the child looked well, the weight increased to 20.9 kg. and there was no evidence of recurrent or metastatic tumor. A mass was felt in the right inguinal region 3 mo. after operation. The child was readmitted to the hospital for further study.

A large, soft lymph node in the right inguinal region was excised. Microscopic examination was reported metastatic malignant teratoma showing carcinomatous structure; many mitoses.

RGs of the skull and long bones showed no abnormality. Chest RG showed no definite evidence of pulmonary infiltration, although both hila and pulmonary markings, particularly at the bases, were prominent.

The child's condition rapidly became worse. A hard nodular mass was felt in the lower abdomen 3½ mo. after operation, increasing in size thereafter. Daily fever was present. Examinations of the blood showed a progressive anemia and leukocytosis. Aminopterin (7 mg.) was given but no change was noted. Examination of the bone marrow 4 mo. after operation revealed a highly cellular, active

FIG. 13. Microscopic section of tumor in Case 3 showing immature epithelial cells (×200).

marrow with numerous megakaryocytes; no tumor cells were seen. The child died 4½ mo. after operation. Permission for necropsy was not obtained.

Comment: In retrospect, roentgen irradiation should have been started immediately after operation for such a highly malignant tumor.

SUMMARY

The histogenesis, pathologic and clinical features, diagnosis and treatment of retroperitoneal teratomas in infancy and childhood, based upon a study of 44 cases, are reviewed. Two cases of benign retroperitoneal teratomas with recovery, and one case of malignant retroperitoneal teratoma with subsequent death are presented.

Retroperitoneal teratomas were usually noted in female infants under the age of 1 year as large, left-sided, abdominal tumors extending into the lumbar region, rarely causing symptoms, and revealing areas of ossification on roentgen examination.

In this series 6.8% of the teratomas had undergone malignant changes, and 29.5% of the tumors were not operated upon and were described at autopsy.

Successful treatment of retroperitoneal teratomas was dependent upon early operation, careful operative technic through a liberal transperitoneal incision, and adequate preoperative and postoperative management. The operative mortality was 29%.

The histologic features constituted an important factor in prognosis: 10 cases of benign retroperitoneal teratoma in infancy and childhood were well for periods of over one year after operation, and no cure of malignant retroperitoneal teratoma has been reported in this age group.

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SPANISH ABSTRACT

Teratomas Retroperitoneales en la Infancia

El autor presenta una revisión de la histogénesis, caracteristícas clínicas y patologicas, diagnósis y tratamiento de los teratomas retroperitoneales en la infancia, basandose en un estudio de 44 casos. Se describen en detalle dos casos de teratomas retroperitoneales benignos y un caso de teratoma maligno con subsequente "exitus fatalis."

Los teratomas retroperitoneales ocurren frecuentemente en niñas menores de un año de edad, presentandose como masas abdominales de gran tamano localizadas en el lado izquierdo, raramente producen sintomas clinicos, y el exámen radiografico revela focos de osificación variables.

En esta serie 6.8% de los teratomas tuvieron degeneración maligna y un 29.5% de los tumores no fueron operados pero descritos en la autopsia.

El éxito del tratamiento de los teratomas retroperitoneales depende en la resección temprana, a tráves de una incisión transperitoneal liberal y en el cuidado pre-y-post-operatorio adecuado. La mortalidad operatoria de esta serie fué 29%.

Las caracteristícas histologícas constituyen un factor importante en el pronóstico: diez casos de teratomas retroperitoneales benignos permanecían aparentemente curados por periodos de más de un año siguiente a la operación, mientras que no curas de teratomas malignos han sido reportadas en niños.

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ABSORPTION OF α-TOCOPHEROL AND TOCOPHERYL ESTERS BY PREMATURE AND FULL TERM INFANTS AND CHILDREN IN HEALTH AND DISEASE

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IT IS generally recognized that premature infants, when compared to full term infants, show impaired capacity to absorb and retain dietary fats. Recent studies of Morales et al.[1] indicate that augmenting the fat content of the diet will increase the net absorption and retention of fat, but will not influence the percentage of the dietary fat absorbed by the premature. Clifford and Weller[2] and others have shown that vitamin A in percomorph oil is likewise poorly absorbed by the premature infant, but that this is not the case when a water-soluble vehicle for the vitamin A is used. Studies of the latter type have been handicapped by the need for blood samples of such size that only a single determination can be made and no curve of absorption obtained.

Application of the micromethod of Quaife et al.[3] for measuring tocopherols in capillary samples of blood offers a means of securing response curves of infants following administration of another fat-soluble vitamin. Vitamin E, or alpha tocopherol, is available both as free and as esterified tocopherol in both the natural and synthetic forms. Of these, only the di-sodium phosphate ester has appreciable water-soluble properties. The response curve of the human adult to given doses of tocopherol has been found by Steinberg,[4] Popper et al.[5] and Klatskin and Krehl[6] to be abnormally low in liver disease. Steinberg[4] finds the same to be true in primary fibrocytis. The response curve is regarded as a reasonable reflection of the efficiency of absorption of a given dose of tocopherol. It probably bears little relation to, and is but little influenced by, the state of tissue storage or utilization of tocopherol. Whatever influence such factors may have is reduced to a minimum in the newborn infants. The studies reported here represent efforts to (1) measure and compare the tocopherol response curve in premature and full term infants, (2) compare the response given by different forms of alpha tocopherol and (3) determine whether certain disease states in older infants significantly influence the absorption of tocopherol.

MATERIALS AND METHODS

Materials: The infants in this study were those admitted to the newborn and premature nurseries of the Strong Memorial and Rochester Municipal Hospitals. All full term infants weighed more than 2500 gm. at birth and all were in good physical condition. Birth weights of the premature infants ranged from 1200 to 2480 gm. and during their hospital stay they received a formula of alacta®, water and carbohydrate. Vitamin supplements in the form of ascorbic acid 50 mg. and oleum percomorophum 10 drops were administered daily after the infant had attained an age of 14 days.

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The older infants and children were admitted to the pediatrics service of the Strong Memorial and Rochester Municipal Hospitals.

Tocopherols* in the form of d-α-tocopherol, d-α-tocopheryl acetate, d-α-tocopheryl acid succinate and the sodium salt of d-α-tocopheryl phosphate were administered in oral doses of 20 mg./kg. body weight. The d-α-tocopherol and the d-α-tocopheryl acid succinate were dissolved in olive oil at a concentration of 100 mg./1 cc. The d-α-tocopheryl acetate was administered as a concentrate containing 280 mg./cc. The prescribed dose of the sodium salt of d-α-tocopheryl phosphate was solubilized in a minimum volume of sterile distilled water prior to administration. A preparation† of dl-α-tocopheryl

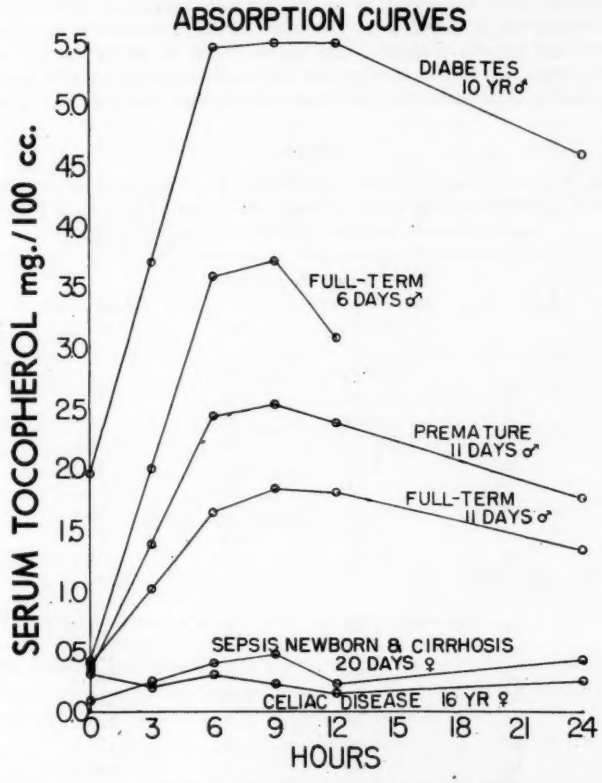

CHART 1. Typical tolerance curves for newborns, infants and children. These data are selected to demonstrate flat curves seen in celiac syndrome and cirrhosis and marked reaction observed in diabetes. Premature and full term infants show "normal" type curve.

acetate, solubilized and sterile, was injected into some of the subjects at a level of 20 mg./kg. body weight. One subject was given an oral dose of dl-α-tocopheryl acetate.‡

* Tocopherols in the form of d-α-tocopherol, d-α-tocopheryl acetate, d-α-tocopheryl acid succinate and the sodium salt of α-tocopheryl phosphate were generously supplied by Dr. Philip L. Harris of Distillation Products Industries.

† Syntopherol®, a solubilized preparation of dl-α-tocopheryl acetate prepared for intramuscular use, was supplied by Abbott Laboratories.

‡ Ephynal®, dl-α-tocopheryl acetate supplied by Hoffman LaRoche Laboratories.

Since the various tocopheryl esters were administered in the same weight dose as the d-α-tocopherol they provide less α-tocopherol on a weight-for-weight basis. From a knowledge of the molecular weights of the various tocopheryl esters 20 mg. of each may be calculated to provide the following weights of α-tocopherol: d-α-tocopheryl acetate 18.2 mg., d-α-tocopheryl acid succinate 16.2 mg. and the disodium salt of α-tocopheryl phosphate 15.5 mg.

Method: The micromethod for assay of total tocopherols as described by Quaife et al.[3] was used. A fasting blood sample was obtained by heel or finger punctures as previously described by Wright et al.[7] and the tocopherol preparation to be tested was administered per os or injected intramuscularly at a level of 20 mg./kg. body weight. Blood samples were subsequently obtained at 3, 6, 9, 12 and 24 hr. after oral administration. On subjects given intramuscular injections of tocopheryl acetate blood samples were obtained also at 36 and 48 hr. The values for the blood levels were plotted as a typical "tolerance curve" and the area under the curve for the 1st 12 hr. of the test was determined by means of a planimeter. This technic superimposed some uniformity on the results and permitted the comparison of relative areas under the curve thus circumventing variations in the contour of the

TABLE 1

FASTING AND 9 HOUR LEVELS OF SERUM TOCOPHEROLS, AREAS UNDER RESPONSE CURVE AND CALCULATED INDICES OF RESPONSE IN PREMATURE INFANTS GIVEN ORAL DOSES OF d-α-TOCOPHEROL AND d-α-TOCOPHERYL ACID SUCCINATE*

Type of Tocopherol	Age in Days	Serum Tocopherol		Area Under Curve	Index of Response†
		Fasting	9 hr.		
		mg./100 cc.	mg./100 cc.	u.	
d-α-tocopherol	2	0.24	0.52	21.7	1.4
	4	0.69	1.88	61.9	5.9
	5	0.22	0.88	34.6	3.3
	6	0.45	2.60	98.5	10.8
	7	0.43	1.86	60.9	7.1
	8	0.20	2.27	70.9	10.3
	8	0.25	3.05	85.0	14.0
	8	0.27	2.74	95.6	12.3
	Aver. 1–10			66.1±27.6	8.1±4.4
	11	1.46	2.37	94.7	4.6
	12	0.60	2.88	104.0	11.4
	13	0.45	3.90	135.1	17.3
	13	1.16	2.58	111.5	7.1
	15	0.80	3.56	128.2	13.8
	17	0.59	3.08	119.0	12.4
	18	1.05	3.66	147.2	13.0
	19	0.18	2.55	86.0	11.9
	19	0.35	2.62	91.5	11.4
	Aver. 11–20			113.0±21.0	11.4±3.8
	25	0.62	2.96	122.6	11.7
	25	0.64	2.60	100.0	9.8
	25	0.54	0.75	37.5	1.0
	27	0.27	3.68	125.5	17.0
	29	0.00	0.00	0.0	0.0
	29	0.08	0.34	10.9	1.3
	29	0.34	3.02	90.3	13.4
	30	0.48	2.65	96.3	10.8
	Aver. 21–30			72.9±46.6	8.1±6.5

TABLE 1—(*continued*)

Type of Tocopherol	Age in Days	Serum Tocopherol		Area Under Curve	Index of Response†
		Fasting	9 hr.		
		mg./100 cc.	mg./100 cc.	u.	
d-α-tocopheryl	3	0.61	2.47	88.0	11.5
acid succinate	3	0.52	2.01	75.7	9.2
	4	0.79	2.20	75.2	8.7
	9	1.16	4.42	160.0	20.4
	10	0.99	5.08	170.7	25.3
	Aver. 1–10			113.9±47.4	15.0±7.5
	11	0.33	2.54	97.5	13.6
	12	0.71	3.38	124.6	16.5
	16	0.26	0.75	36.5	3.0
	17	0.42	2.21	69.0	11.1
	17	0.60	1.87	63.2	7.9
	Aver. 11–20			78.2±33.8	10.4±5.2
	21	0.65	3.14	104.5	15.4
	23	0.23	2.62	87.5	14.8
	24	0.32	2.56	89.0	13.8
	26	0.25	2.14	71.3	11.7
	Aver. 21–30			88.1±13.6	13.9±1.6

* Both preparations given orally as single doses of 20 mg./kg. body weight. On a molar weight basis, the succinate ester would provide 16.2 mg. of free d-α-tocopherol.

† $\text{Index} = \dfrac{(\text{9 hr. Level} - \text{Fasting Level}) \times 100}{\text{Tocopherol mg./kg. Body Weight}}$

absorption curves. Typical tolerance curves are shown in chart 1. Since the Emmerie-Engel reaction by which the serum tocopherols are quantitated fails to measure the esterified forms of α-tocopherol the serum tocopherol levels determined after the oral administration of tocopheryl esters represent increments in free α-tocopherol.

Since the serum level of tocopherol following an oral dose was at a maximum 9 hr. after administration of free or esterified tocopherols, an index which accounted for the actual amount of free tocopherol ingested was calculated. This index was arbitrarily defined as follows:

$$\text{Index} = \frac{(\text{serum tocopherol at 9 hr.} - \text{serum tocopherol fasting}) \times 100}{\text{mg. free tocopherol administered/kg. body weight}}$$

The denominator had values of 20, 18.2 or 16.2, respectively, if d-α-tocopherol, d-α-tocopheryl acetate or d-α-tocopheryl acid succinate were given.*

* Esters of α-tocopherol have been shown to possess greater biologic potency than free tocopherol, on the basis of tocopherol equivalents, as evaluated by the rat bioassay test. This difference is attributed to increased resistance of the esters to autoxidation in the gastrointestinal tract. On the basis of data presented by Harris and Ludwig,[8] the biologic values for the administered doses of d-α-tocopherol, d-α-tocopheryl acetate and d-α-tocopheryl acid succinate, expressed as international units, would be 18.4, 24.2 and 27.2 I.U., respectively. However, since there exists no evidence that the factors responsible for the differences exist in, or would be reflected in the serum tocopherol levels of, the premature or older infant, no allowance has been made for the factor of biologic potency in the calculations presented here.

Results and Discussion

Table 1 presents the data on relative oral absorption of d-α-tocopherol and d-α-tocopheryl acid succinate in 39 premature infants, grouped according to age periods. The initial and nine hour serum levels of tocopherol are given here in the hope that other investigators may find these absolute data of more value than the more arbitrary areas under the curve. The latter, expressed as planimeter units under the response curve covering the 12 hour period following a single oral dose (20 mg./kg. body weight) of the tocopherol prepara-

TABLE 2

Fasting and 9 Hour Levels of Serum Tocopherols, Areas Under Response Curve and Calculated Indices of Response in Full Term Infants Given Oral Doses of α-Tocopherol or Tocopheryl Esters*

Type of Tocopherol	Age in Days	Serum Tocopherol		Area under curve	Index of response†
		Fasting	9 hr.		
		mg./100 cc.	mg./100 cc.	u.	
d-α-Tocopherol	1	0.31	1.19	45.0	4.4
	3	0.35	1.46	37.7	5.6
	6	0.21	2.38	75.7	10.9
	6	0.40	3.72	141.9	16.6
	9	0.61	3.70	136.7	15.4
				Aver. 87.4±49.5	Aver. 10.6±5.5
d-α-Tocopheryl acid succinate	8	0.42	2.22	77.8	11.1
	9	0.63	1.97	82.7	8.3
	11	0.37	1.84	71.5	9.1
	12	0.56	2.70	113.2	13.2
				Aver. 86.3±18.5	Aver. 10.4±2.2
d-α-Tocopheryl acetate	5	0.36	1.08	36.8	4.0
	27	1.16	1.31	66.7	0.8
dl-α-Tocopheryl acetate (Syntopherol ®, I.M.)	6	0.60	1.72	70.7	6.2
	25	0.20	1.22	46.5	5.6

* Given orally as single doses of 20 mg./kg. body weight, except for syntopherol ® which was given at same dosage intramuscularly. In the case of d-α-tocopherol, d-α-tocopheryl acid succinate and d-α-tocopheryl acetate, respectively, this represented 20, 16.2 and 18.2 α-tocopherol equivalents.

† Index = $\frac{\text{(9 hr. Level} - \text{Fasting Level)} \times 100}{\text{Tocopherol mg./kg. Body Weight}}$

tions, indicate that the free and esterified tocopherols are absorbed with about equal effectiveness in each age group. The values calculated for the standard deviation mask any differences one might expect to see between the free and ester forms due to the lesser amount (16.2 mg.), or possibly greater biologic effect, of tocopherol provided as the ester. For the age group 1 to 10 days, in which the greatest differences occur, the mean planimeter values of 66.1 and 113.9 were not statistically significant since students "t" value was 1.735 and $P = 0.11$.

Considering the calculated indices in table 1, which correct for differences in the amounts of α-tocopherol provided by the two preparations, there also appears to be no significant difference in the effectiveness of absorption of the tocopherol provided by the two preparations.

When the data are examined for the influence of age on the ability of the premature infant to utilize or absorb tocopherols, only the mean planimeter values of 66.1 and 113.0 for infants given d-α-tocopherol in the age groups 1 to 10 days and 11 to 20 days represent differences which are statistically significant. Students "t" test gave a t of 3.45 with a P of < 0.01. On the other hand, the difference in average index of response in these same groups is not statistically significant. In general, age appears to have little or no influence on the response of the infant to oral tocopherol as determined by a 12 hour tolerance test.

Table 2 summarizes the data for a series of 13 full term infants. It will be noted that the absorption response, whether evaluated as planimeter units under the curve or as the calculated index, was essentially the same for d-α-tocopherol as for the d-α-tocopheryl succinate, and also quite comparable to the response shown by premature infants (table 1). Absorption data on the acetate ester of natural α-tocopherol given orally, and the acetate ester of synthetic α-tocopherol given intramuscularly, though limited as to number, are in accord with those given by the other tocopherol preparations. It seems reasonable to conclude that, within the limits of the methods employed, premature and full term infants show no significant difference in their capacity to absorb natural α-tocopherol, whether it be provided as free tocopherol or as the acid succinate ester. This stands in contrast to the reported lesser effectiveness of absorption (and/or retention) of vitamin A and of fats in general in prematures when compared to full term infants. Chart 1 shows typical response curves on premature and full term infants.

The studies of Wright et al.[7] indicate that because of limited placental transfer of vitamin E newborn infants possess rather low levels of serum tocopherols which are readily augmented in breast-fed infants, due to more effective mammary transfer of the vitamin. The data presented in the present report support and extend these observations, by demonstrating that premature infants (which are rarely breast-fed) can absorb and presumably retain tocopherols as effectively as the full term infant; they also suggest certain differences between tocopherol on the one hand, and vitamin A and fats on the other hand, in the changing pattern of lipid metabolism in the prenatal and neonatal periods.

Chart 2 summarizes the data obtained on a series of 29 older infants given various tocopherol preparations at 20 mg./kg. weight. The response of the infant to the test is expressed in terms of planimeter units or area under the curve for a 12 hour test period. If a response of 60 planimeter units is arbitrarily selected as the minimum normal value of performance, a reduced absorption of tocopherol is noted in cases of diarrhea, biliary obstruction, fibrocystic disease, cirrhosis and some types of malnutrition. The data for the infant with first degree burns and the infant convalescing from pneumonia are probably within normal limits of variation. It is of interest to note the change in response in the case of fibrocystic disease following active therapy with pancreatin. The apparent poor response to the α-tocopheryl phosphate by an infant with a subdural hematoma, known to have a good reaction to other tocopherol preparations is probably due to the ease with which this compound forms an insoluble calcium salt and is eliminated in the stool. The response of a 20 day old infant with sepsis and cirrhosis is shown in chart 1.

The fasting and nine hour serum levels of tocopherol and the calculated indices for the infants shown in chart 2 are given in table 3. The data serve again to measure in a somewhat different fashion the response of the infant to an oral or intramuscular dose of tocopherol or its esters. An index of 4.2 or less is found to correspond with the arbitrarily selected value of 60 planimeter units below which an inadequate response to

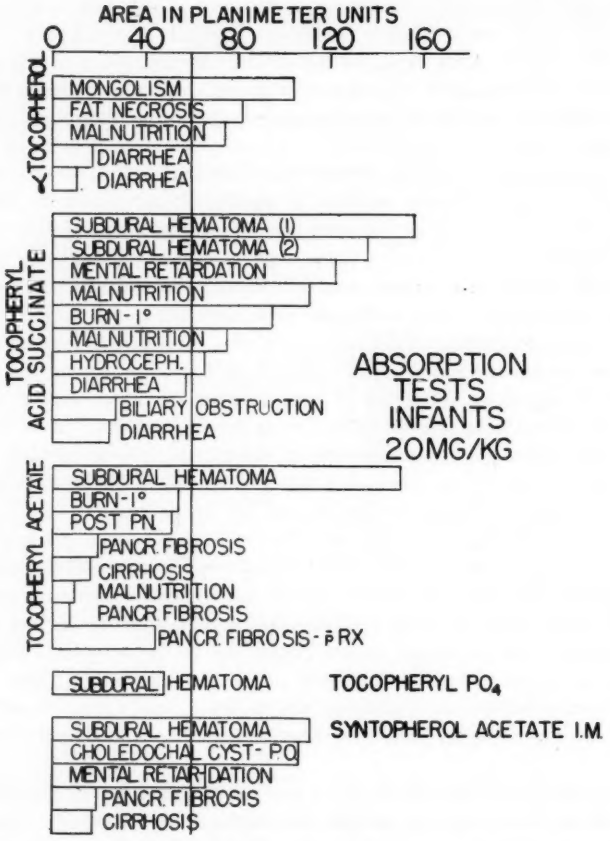

CHART 2. Area under curve response of infants given various types of tocopherol at 20 mg./kg. body weight, orally.

the absorption of tocopherol was thought to be manifest. The low and frequently negative indices associated with fibrocystic disease, diarrhea and malnutrition are evident. Subject S.S., tested on both the acid succinate and acetate forms of tocopherol, was found to have a negative index with the latter compound. The area associated with this latter test was 54 planimeter units and the blood levels of 1.25 and 1.04 mg./100 cc. serum tocopherol at 0 and 9 hours indicate a "flat type" curve.

The poor response of a patient with fibrocystic disease and a patient with cirrhosis to

TABLE 3

FASTING LEVELS AND 9 HOUR LEVELS OF INFANTS GIVEN α-TOCOPHEROL OR ITS ESTERS, ORALLY, AT 20 MG./KG. BODY WEIGHT

Subject	Diagnosis	Type of Tocopherol	Serum Tocopherol		Index
			Fasting	9 hr.	
			mg./100 cc.	mg./100 cc.	
L.M.	Mongolism	α	0.22	2.05	9.1
C.C.	Fat necrosis	α	0.21	2.45	11.2
K.C.	Malnutrition	α	0.91	1.88	4.9
L.G.	Diarrhea	α	0.18	0.37	1.0
L.M.	Diarrhea	α	0.22	0.23	0.1
A.P.	Subdural hematoma	Succinate	1.23	3.18	12.0
A.P.	Subdural hematoma	Succinate	1.83	3.48	10.2
B.S.	Mental retardation	Succinate	0.64	2.75	13.0
P.T.	Malnutrition	Succinate	0.91	2.85	12.0
S.S.	1° Burn	Succinate	1.03	2.27	7.9
K.C.	Malnutrition	Succinate	0.54	2.61	12.8
D.W.	Hydrocephalus	Succinate	0.25	1.72	9.1
R.R.	Diarrhea	Succinate	0.52	1.20	4.2
D.C.	Biliary obstruction	Succinate	0.42	0.41	−0.1
L.G.	Diarrhea	Succinate	0.13	0.43	1.8
A.P.	Subdural hematoma	Acetate	1.98	3.70	9.5
S.S.	1° Burn	Acetate	1.25	1.04	−1.1
R.B.	PNC—convalescent	Acetate	0.84	1.19	1.9
J.S.	Fibrocystic disease	Acetate	0.11	0.54	2.4
B.C.	Cirrhosis	Acetate	0.09	0.47	2.1
K.C.	Malnutrition	Acetate	0.44	0.09	−1.9
E.D.	Fibrocystic disease	Acetate	0.24	0.10	−0.8
E.D.	Fibrocystic $\overline{pR}_x$	Acetate	0.58	0.86	1.5
A.P.	Subdural hematoma	Phosphate	0.56	1.14	3.7
A.P.	Subdural hematoma	Syntopherol ®	1.19	2.75	8.6
M.M.	Choledochal cyst P.O.	Syntopherol ®	1.35	2.46	6.1
M.W.	Mental retardation	Syntopherol ®	0.83	1.91	5.9
E.D.	Fibrocystic disease	Syntopherol ®	0.04	0.50	0.3
B.C.	Cirrhosis	Syntopherol ®	0.06	0.50	0.2

an intramuscular injection of α-tocopheryl acetate is evident by both area measurements and indices. These data may reflect a marked diminution in the rate of absorption of tocopherol from an intramuscular site or may be due to failure to quantitate the ester form which may be the dominant type of tocopherol in the blood stream under these conditions.

The data summarized in chart 3 represent observations on 14 children ranging in age from 2 to 16 years. Areas of less than 60 planimeter units are noted in a case of lupus erythematosis and a case of celiac syndrome. After a course of therapy with cortisone the case of lupus erythematosis was observed to have a normal tolerance curve. This increase in performance was accompanied by an elevation in the blood carotenoids rising from

TABLE 4

FASTING LEVELS AND 9 HOUR LEVELS OF SERUM TOCOPHEROLS IN CHILDREN GIVEN ORAL DOSES OF TOCOPHERYL ACETATE AT 20 MG./KG. BODY WEIGHT

Subject	Diagnosis	Type of Tocopherol	Serum Tocopherol		Index
			Fasting	9 hr.	
			mg./100 cc.	mg./100 cc.	
D.E.	Diabetes	Acetate	1.96	5.50	19.5
L.H.	Giardiasis; Hypothyroid	Acetate	1.72	4.72	16.5
G.R.	Diabetes; Hepatomegaly nephrosclerosis	Acetate	2.04	3.21	6.4
D.T.	Nephrosis	Acetate	2.08	3.42	7.4
R.D.	Conv. rheumatic fever	Acetate	1.11	2.95	10.1
R.H.	Sexual precocity	Acetate	1.07	2.94	10.3
G.P.	Aseptic necrosis	Acetate	1.65	1.60	−0.3
A.L.	Post-poliomyelitis	Acetate	0.73	2.62	10.4
E.D.	Angiofibroma	Acetate	0.79	1.40	3.4
H.S.	Lupus	Acetate	0.65	0.68	0.2
H.S.	Lupus p cortisone	Acetate	1.55	2.60	5.9
R.L.	Fibrocystic disease	Acetate	0.36	0.44	0.4
T.T.	Celiac	Acetate	0.30	0.21	−0.5
T.T.	Celiac	Solubilized acetate	0.06	0.36	1.6
H.S.	Lupus	Syntopherol ®	0.47	0.66	1.0
S.M.	Sprue	Ephynal ®	0.25	0.58	1.8

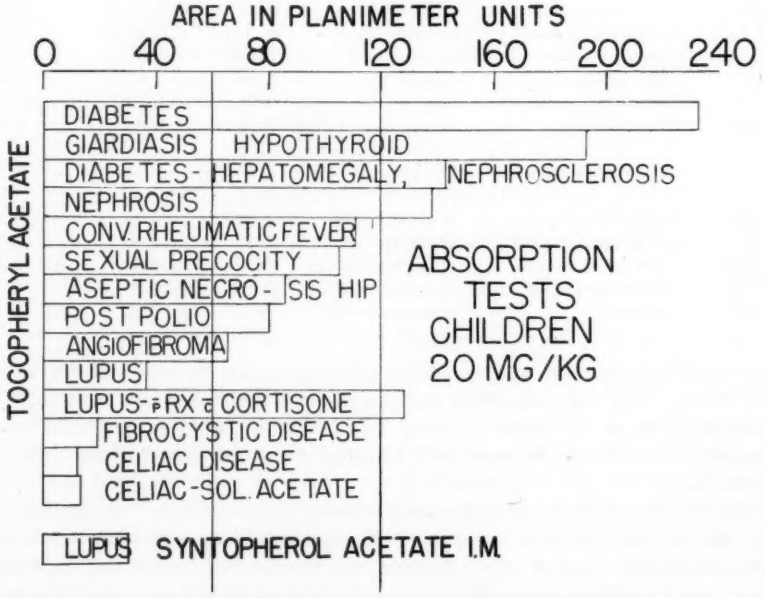

CHART 3. Area under curve response of children given α-tocopherol acetate at 20 mg./kg. body weight, orally.

30γ/100 cc. of serum before cortisone therapy to 70γ/100 cc. of serum after cortisone therapy. Thorn et al.[9] have reported an elevation in the serum vitamin A following treatment with ACTH.

. The upper limits of response to a tocopherol absorption test may be seen in this series. If one selects arbitrarily 120 units as the peak of normal response, metabolic disturbances such as diabetes or nephrosis which are accompanied by hypercholesterolemia have an associated tocopherolemia and therefore a greater area under the curve. In chart 1 the tolerance curves for a patient with diabetes and a patient with celiac syndrome are shown.

TABLE 5

COMPARISON OF VITAMIN E TOLERANCE TESTS WITH VITAMIN A TOLERANCE TESTS

			Serum Tocopherol mg./100 cc. Serum				Serum Vitamin A u./100 cc.		
Subject	Age	Clinical Diagnosis	Type of Tocopherol	Fasting	9 hr. Level	Area u. Planimeter	Type of Vitamin A	Fasting	4½ hr. Value
L.G.	2 mo.	Diarrhea	α	0.18	0.37	16.7	ester	21	105
L.G.	2½ mo.	Diarrhea	Succinate	0.13	0.43	23.9	—	—	—
J.S.	15 mo.	Cystic fibrosis of pancreas	Acetate	0.11	0.54	19.1	ester	27	16
J.S.	15 mo.	Cystic fibrosis of pancreas	—	—	—	—	alcohol	27	136
E.D.	21 mo.	Cystic fibrosis of pancreas	Acetate	0.24	0.10	6.8	ester	11	11
E.D.	21 mo.	Cystic fibrosis of pancreas	Acetate	0.58	0.86	42.6	alcohol	11	69
L.H.	2 yr.	Giardiasis hypothyroid	Acetate	1.27	4.72	193.0	ester	0	179
R.L.	5 yr.	Cystic fibrosis of pancreas	Acetate	0.36	0.44	18.8	ester	22	31
T.T.	16 yr.	Celiac	Acetate	0.30	0.21	11.5	ester	16	6
T.T.	16 yr.	Celiac	Solubilized acetate	0.06	0.36	13.3	ester	16	20
S.M.	26 yr.	Sprue	Acetate	0.25	0.58	24.8	ester	15	22

The response of a 26 year old woman with sprue, the sister of the child with the celiac syndrome, was abnormal. The area determined had a value of 24.8 units.

The data in table 4 present the fasting and nine hour levels of serum tocopherol with the calculated indices for the series of children represented in chart 3. The high indices associated with diabetes and hypothyroidism are evident. The negative index of −0.3 for a patient with aseptic necrosis of the hip despite an area of 86 planimeter units may be explained by the relatively high blood levels of tocopherol at both 0 and 9 hours, indicative of little or no absorption of tocopherol, but an elevated area due to the displacement of these points on the y axis of the tolerance curve. The findings reported here are in accord with the tolerance curves observed by Steinberg,[4] Popper et al.[5] and Klatskin and Krehl[6] in adults with primary fibrositis, cirrhosis and obstructive jaundice. It is not yet clear whether these low tolerance curves represent defective intestinal absorption alone or also reflect other metabolic dysfunctions influencing the fate of tocopherol once it has passed the intestinal barrier.

A comparison of vitamin A absorption tests with vitamin E absorption tests is made in table 5. These data indicate that those disease states of infants and children associated with a poor or diminished vitamin A tolerance curve also exhibit an impaired absorption of tocopherol. The response of subject L.G. to the vitamin A tolerance was questionable, i.e., a 4½ hour value 105 IU of A is a borderline response.

Thus the tocopherol absorption test may be used to demonstrate the impaired absorption of fat and fat-soluble vitamins by patients with fibrocystic disease, celiac syndrome and some cases of diarrhea. As used in this study the tocopherol absorption test has some advantages over the vitamin A absorption test. The serum sample required is small (0.06 cc.), the laboratory manipulations are minimal, and the error in the method is 5% or less. In addition serum tocopherols are sufficiently stable to light, room temperature and deep-freeze storage that these advantages permit shipment and storage of serum samples and aid in the collection of field survey data.

Summary

The ability of premature and full term infants in health and disease to absorb vitamin E (tocopherol) was determined using the technic of multiple withdrawals of small samples of capillary blood at three hour intervals following an oral dose of α-tocopherol or α-tocopheryl esters.

Premature infants were found to absorb vitamin E as well as full term infants, when compared on the basis of the area under the curve for a 12 hour period following an oral dose of tocopherols at 20 mg./kg. body weight. This is in marked contrast to the diminished ability of the premature infant to utilize vitamin A and fats.

In a series of 29 infants, those disease states diagnosed as fibrocystic disease of the pancreas, diarrhea and cirrhosis were characterized by a poor response to the test, i.e., the tolerance curve was low. Others, infants with a variety of disorders not associated with fat or fat-soluble vitamin intolerance, had characteristic absorption curves with a maximum nine hours after receiving oral tocopherol.

In a series of 14 children and 1 adult, patients with sprue, celiac syndrome and lupus erythematosis were noted to absorb tocopherols poorly. Metabolic disorders with associated hypercholesterolemia were observed to give abnormally high values for the area under the curve.

A comparison of vitamin A absorption with vitamin E or tocopherol absorption in a series of 10 observations indicated that patients responding poorly to one test did poorly in both.

No difference in response was noted when various esterified forms of tocopherol were administered in place of α-tocopherol. This is contrary to the reported increase in biologic potency (rat assay) of the esterified forms of tocopherol.

An index calculated from the fasting and nine hour levels of serum tocopherol which corrected for the tocopherol equivalents supplied by the ester forms compared favorably with the area measurements and failed to demonstrate any difference in absorption of the free versus ester tocopherol.

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SPANISH ABSTRACT

La Absorción de α-Tocopherol y Tocopheryl Esters por Prematuros y Niños a Termino

Se determinó la propiedad de los prematuros y niños a termino (sanos y enfermos), en absorber la vitamina E (tocopherol) usando la técnica de determinaciones seriadas en pequeñas cantidades de sangre capilar a intervalos de tres horas siguientes a la administración de una dosis por via oral de α-tocopherol o de tocopheryl esters.

Se observó que los prematuros absorben la vitamina E tan bien como los niños a termino, cuando se comparan utilizando una curva de absorción por un periodo de 12 horas siguientes a la administración oral de una dósis de tocopherol (20 mg./kg. de peso). Esto contrasta notablemente con la pobre utilización de vitamina A y de grasas por los prematuros.

En una serie de 29 niños, aquellos casos diagnosticados como enfermedad cistica-fibrosa del pancreas, diarreas y cirrosis, se caracterizaron por una repuesta pobre en la absorción, es decir por curvas de tolerancia bajas. Otros casos con alteraciones variables, no asociadas con intolerancia a grasas o vitamínas solubles en grasas, presentaron curvas de absorción caracteristicas, con un máximo de absorción a las nueve horas siguientes a la administración oral del tocopherol.

En una serie de 14 niños y un adulto, con diagnosticos de sprue, enfermedad celiaca, y lupus eritematosus, se caracterizaron por una absorción pobre de tocopherol. Se observaron valores anormalmente altos de absorción en los desórdenes metabolicos asociados con hipercolesterolemia.

La comparación de la absorción de vitamína A con la absorción de vitamína E o de tocopherol, indicó que pacientes que respondian pobremente a una prueba, lo eran a la otra.

No se encontraron diferencias en la repuesta de absorción cuando el α-tocopherol fué substituido por varias formas esterificadas de tocopherol. Esto es contrario a el reportado aumento de potencia biologica (rat assay) de las formas esterificadas del tocopherol.

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ANEURYSMS OF THE SINUSES OF VALSALVA

With Report of a Case

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ANEURYSMS of the sinuses of Valsalva or aortic sinuses, while always unusual, are recognized with some degree of frequency in adults. Their occurrence in children is, however, unusual; when present they usually give rise to symptoms only after childhood, and the occurrence of rupture of an aneurysm of this type in a young child is thought to be unique.

Aneurysm of the sinuses of Valsalva was first described in detail in 1840 by Thurman[1] who recognized rupture as a complication. Since that time discussions have dealt primarily with the disease as seen in adults, in whom it is usually of luetic origin. However, Abbott[2] in 1919 was able to collect several cases of apparent congenital etiology. Among these was the case of von Krzywicki, a 20 year old female who died nine months after the presumed time of rupture of an aneurysm of the right aortic sinus into the right ventricle; also recorded was the case of Hale-White of a similar ruptured aneurysm accompanied by an interventricular septal defect in a 15 year old male who had had symptoms for four months before death. Further review of the literature has revealed only one additional possible case of congenital aneurysm with rupture in the age group under 21. Ramsey and Mosquera[3] reported the case of a six year old female child with a known "loud murmur" over the base of the heart three years before death. Subacuate bacterial endocarditis supervened eight months before death. After apparent recovery sudden death ensued attributed to the rupture of an aortic cusp. Necropsy revealed an endocardial-lined communication from a dilated right sinus of Valsalva to the right ventricle, evidence of an old endocarditis and a freshly ruptured aortic leaflet. Thus, there remains some room for doubt as to whether this actually represented an old ruptured aneurysm of either congenital or mycotic etiology or a congenital communication between the aorta and right ventricle such as has been described by several investigators.[2, 4]

While these reports have dealt primarily with aneurysms of a single sinus, simultaneous aneurysms of congenital origin of all three sinuses have been described in the adult.[5]

Three aortic sinuses are recognized, but the method of nomenclature is subject to considerable variation. The simplest method consists of identifying the sinus according to its corresponding coronary artery: thus, the right coronary arises in the right sinus of Valsalva, also referred to as the right anterior, anterior or septal sinus; the left coronary arises in the left sinus, sometimes called the left lateral or left posterior sinus; and the third sinus, which is blind, may be identified as the posterior or noncoronary sinus, though it is also described as the right lateral or right posterior sinus.

Since many of the clinical features exhibited by expanding and dissecting aortic aneurysms depend upon involvement of surrounding structures, it may be of value to

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point out certain significant relationships of these sinuses. In general, they are located at the base of the aorta and are bounded by the opposing walls of the aortic semilunar valves and the internal wall of the aorta. The right sinus of Valsalva is in close relationship to the interventricular septum, thus accounting for the tendency of aneurysms of this sinus to burrow into and rupture through the membranous portion of the septum. The posterior or noncoronary sinus lies anterior to the right and left atria; therefore aneurysms of this sinus may rupture into either atrium as well as the right ventricle, pulmonary artery, pericardial cavity and superior vena cava. The left sinus is unique in having extracardiac relationships in its posterior half. Therefore an aneurysm in this location may show itself roentgenographically as a bulge to the left of the pulmonary artery.[6,7] Because of these relationships rupture in the posterior half of this sinus is likely to produce cardiac tamponade by pericardial bleeding while rupture in the anterior half may establish a communication with the pulmonary artery or outflow tract of the right ventricle.

Pathogenesis

In the adult, aneurysms may develop in the aortic sinuses as an extension of syphilitic aortitis, from arteriosclerotic involvement of the aorta, infrequently from mycotic etiology, and occasionally from a congenital weakness of the aortic wall bounding the sinuses. This weakness develops following a faulty shift in the aortic septum during its migration.[8,9] If no shift occurs, transposition of the great vessels is the end result; when the shift is incomplete, a ventricular septal defect with an overriding aorta results, as in an Eisenmenger's complex. When the shift is more nearly complete, the membranous portion of the interventricular septum is formed but lies in a transverse position exposed to the diastolic shock of the aortic blood column.

In the latter instance the incessant pounding of the aortic blood stream leads to the gradual development of an aneurysm at the point of weakness, and eventually dissection occurs in a path determined to some extent by the position of the aneurysm. During this time symptoms may arise as a result of impingement by the aneurysm upon adjacent structures, although more often this period is symptom-free. Burrowing of an aneurysm into the membranous portion of the interventricular septum may cause conduction disturbances.[10,11] By involvement of the ostia of the coronary arteries or by pressure upon the coronary tree, the aneurysm may give rise to myocardial ischemia.[7,11,12] Pressure of an aneurysm, especially of the left aortic sinus, exerted upon the pulmonic orifice may cause clinical pulmonic stenosis and insufficiency.

After a variable period of time the aneurysm may rupture, sometimes as the result of exercise, but often without an immediate precipitating cause. Since rupture of these aneurysms is usually intracardiac, immediate death is not likely to occur unless the point of rupture is large and overwhelming failure ensues. Tricuspid insufficiency often develops if the point of rupture is near the septal leaflet of this valve.

The following case report is that of a 4 year old living child in whom the diagnosis of rupture of an aneurysm of the right sinus of Valsalva into the right ventricle has been tentatively established by clinical and laboratory evidence.

Report of Case

Present Illness: B. P., a 4 yr. old Negro female child, was admitted to Shreveport Charity Hospital with a chief complaint of "fever and spasms." The present illness had begun suddenly the previous evening without apparent exciting cause. The child suddenly jumped out of bed "with a spasm" and vomited. Tachycardia was noted but no cyanosis. Hands and jaws were clenched and

eyes rolled back, but there was no apparent loss of consciousness and the attack subsided within a few minutes. Because of recurring similar attacks throughout the night accompanied by dyspnea and orthopnea, she was brought to the hospital by the mother the following morning.

Family History: In early adult life the mother had been told by a doctor that she had mild diabetes mellitus. No history of syphilis or heart disease was elicited.

Birth History: This pregnancy was uncomplicated except for vomiting throughout. The child weighed 4.1 kg. at birth and was the largest of 3 children born to the mother.

Past History: Growth and development presented no unusual features. The child had been seen routinely in well baby clinics for immunizations during the 1st 2 yr. of life. No cardiac abnormalities

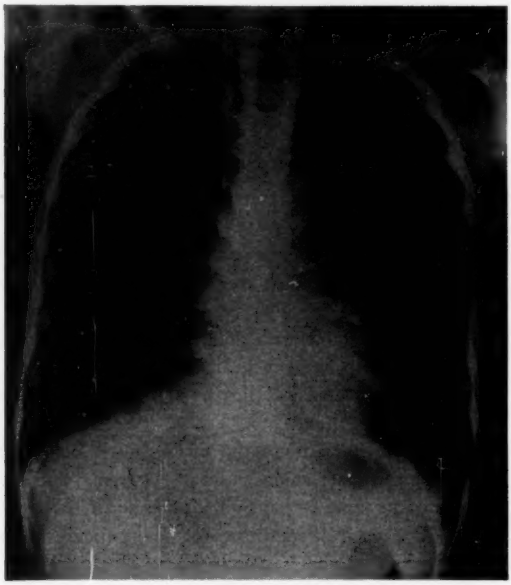

FIG. 1. Chest plate revealing area of pneumonitis in right lung base. Note elongation of outflow tract of left ventricle.

were ever reported to the mother although she does not distinctly remember whether a cardiac examination was ever carried out by a physician.

Evaluation of exercise tolerance was somewhat confusing. The mother stated that the child had never participated in extended or violent exercise with other children, preferring more sedentary forms of amusement. She further stated that the child "has never been a good hand at walking" and frequently demands to be carried. The child is said to be of introverted tendencies, not caring to associate with other children and preferring to play alone.

Physical Examination: On admission the patient weighed 19 kg. Temperature was 38.3° C.; pulse was 122/min. and respiratory rate was 35/min. Blood pressure was recorded as 112 mm.Hg systolic and 72 mm.Hg diastolic. Nutrition and development were within normal limits. Generally she appeared acutely ill and in respiratory distress, with moderate tachypnea and dilatation of the alae nasi. The right tympanic membrane was slightly injected as were the tonsils and pharynx. Percussion note was impaired over the right lower lung field and fine moist rales were heard in this area.

Examination of the heart showed the point of maximal impulse displaced to the seventh left intercostal space just medial to the midclavicular line. A forceful thrill could be felt at the apex and adjacent area. One observer described a gallop rhythm with loud harsh systolic and diastolic murmurs at the fourth left interspace and a systolic murmur at the apex transmitted to the left axilla.

Examination of the abdomen revealed moderate muscular spasm. The liver was palpated 6 cm. below the right costal margin and there was a slight dependent pitting edema.

More critical examination later revealed that both murmur and thrill were quite superficial and were continuous in nature; the murmur was loud, harsh and machinery-like, best heard in the sixth left interspace adjacent to the sternum and not well transmitted in any direction. Initially there was diastolic accentuation but this was replaced later by systolic or systolic and diastolic accentuation.

Laboratory Data: Hgb. was 10.5 gm./100 cc.; leucocyte count was 8.7 thousand/cmm. of which 76% were neutrophiles. Blood culture, sickle cell preparation and serologic tests for syphilis were negative. Blood NPN was 25.8 mg./100 cc.; erythrocyte sedimentation rate was 23 mm./hr. (Cutler method). Chest film revealed no definite abnormality of the cardiac silhouette although it appeared

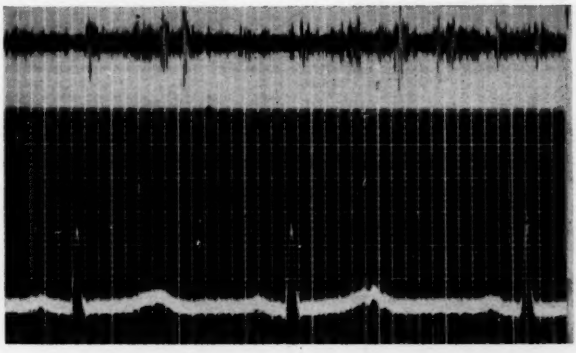

FIG. 2. Sound tracing shows presence of continuous murmur in sixth left interspace.

suggestive of elongation of the outflow tract of the left ventricle. There was an area of increased density in the right lower lung field interpreted as pneumonia (Fig. 1). Electrocardiogram 5 days after admission was interpreted by Dr. Richard Ashman as follows:

"The rate, auricular and ventricular, is 125 per minute; P.R. 0.11 sec.; QRS 0.07 sec. Low T waves in leads I, II, III, and CF IV. The low T waves can be ascribed to the tachycardia in a child of this age. There is no positive evidence of myocardial disease."

Sound tracing 5 days after admission (Fig. 2) revealed a continuous murmur with diastolic accentuation. Fluoroscopy at this time indicated some elongation of the outflow tract of the left ventricle, confirmed by subsequent examinations. Angiocardiograms were nonrevealing.

CLINICAL COURSE

No specific therapy was instituted except penicillin for the respiratory infection and oxygen by nasal catheter. Response was rapid, the respiratory rate returning to normal within 24 hr. and temperature curve within 72 hr. The child was completely asymptomatic by the end of the first week but penicillin therapy was continued throughout the first 30 days of hospitalization. Activity was gradually instituted and well tolerated. Despite the asymptomatic clinical condition, the cardiac thrill and murmur remained essentially unchanged. On the basis of the findings previously listed and particularly the duration and location of the murmur, a clinical diagnosis of rupture of an aneurysm of a sinus of Valsalva was considered and the child was transferred to New Orleans Charity Hospital for further cardiac studies 6 mo. after original admission.

Examination at the time of transfer showed little change in the previously mentioned cardiac findings. An additional significant historical fact was voluntered by the mother at this time; *viz.*, that she had detected without aid a "ring" (thrill) in the patient's chest soon after her initial hospitalization. She further stated that this "ring" had definitely not been present before the child's illness.

Fluoroscopy revealed a normal cardiac silhouette except for minimal elongation of the outflow tract of the left ventricle. Pulmonary vascular markings were not increased. ECG (Fig. 3) was interpreted by Dr. Ashman as follows:

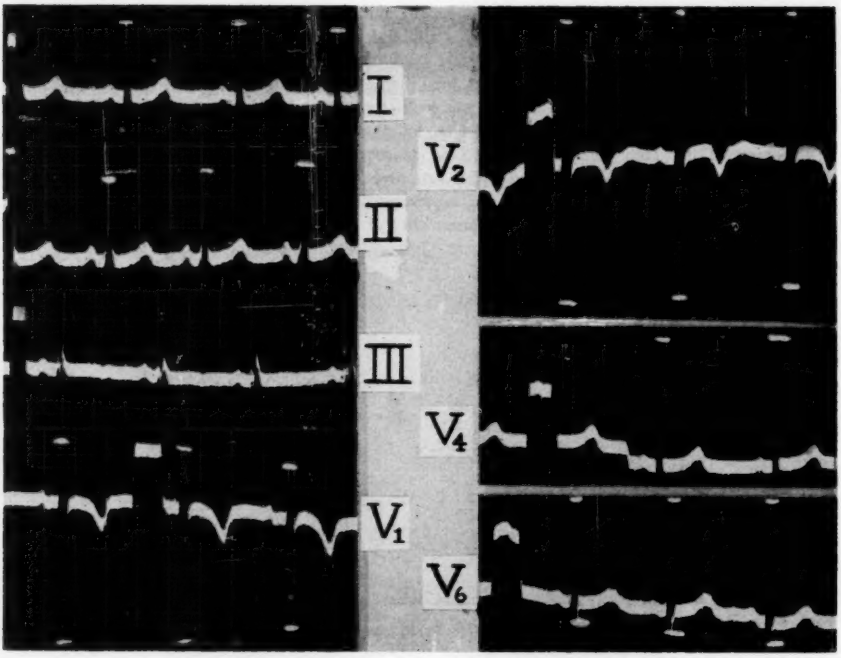

FIG. 3. ECG suggests possibility of slight hypertrophy of left ventricle (cf. text). Short white lines indicate extent of QRS complexes.

TABLE 1

RESULTS OF CARDIAC CATHETERIZATION AND ARTERIAL PUNCTURE

Source of Sample	Activity of Patient	Inspired Gas	Oxygen Content (vol. %)*	Pressure†
Femoral artery	Struggling	Air	16.2 (91% saturation)‡	117/76
Femoral artery	Struggling	100% oxygen	18.3 (100% saturation)	
Superior vena cava	Sleeping (i.v. sodium pentothal)	Air	10.9	
Right atrium	Sleeping	Air	10.9	
Right ventricle	Sleeping	Air	12.5	32/0
Main pulmonary artery	Sleeping	Air	12.2	32/18
Right pulmonary artery	Sleeping	Air	11.7	

* Analyses carried out by a modified Roughton-Scholander technic.[13]

† Measured from a point one-third of the distance between patient's chest and back with patient supine.

‡ The oxygen capacity of all samples was 17.6 vol. %.

"Rate is 90 per minute. P.R. interval is 0.12 sec., QRS 0.08 sec. The slight widening in the base of the R waves in leads I and II and the high R and associated fairly deep S in lead V_2 suggests the possibility of slight hypertrophy of the left ventricle."

Further studies undertaken in an effort to confirm the clinical diagnosis included cardiac catheterization and arterial oxygen analyses. Results are tabulated in table 1.

Pressures obtained at the time of cardiac catheterization and arterial puncture tended to be slightly high. Femoral pressure was recorded at 117/76. Pulmonary artery and right ventricular pressures are shown in figure 4. Oxygen uptake determined by the Benedict-Roth apparatus was 180 cc./min.

Since the child's condition had apparently become stabilized, she was discharged to be followed on an outpatient basis. On her last clinic visit, approximately 10 mo. following the time of presumed rupture of the aneurysm, her condition remained as last described. She is active and shows no apparent incapacitation from her cardiac lesion. Thrill and murmur remain unchanged.

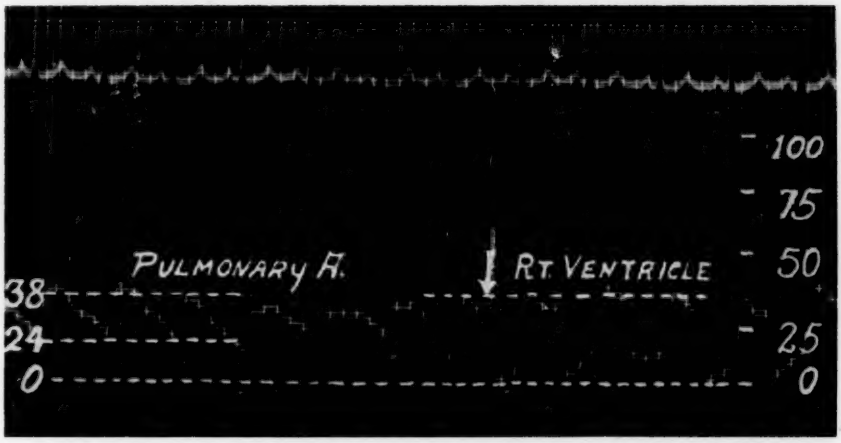

FIG. 4. Continuous strain gauge pressure tracing recorded while catheter was withdrawn from pulmonary artery into right ventricle.

INTERPRETATION OF FINDINGS OBTAINED BY CATHERIZATION AND ARTERIAL PUNCTURES

The arterial blood sample drawn while the patient was struggling and breathing atmospheric oxygen was 91% saturated. This falls within the range of normal values obtained by the authors' laboratory with the technic used. When 100% oxygen was substituted for normal atmosphere, the arterial saturation rose to 100% with an additional 0.7 vol. % carried in physical solution. Again these figures are within the observed normal range for this laboratory and indicate that no veno-arterial shunt is present.

Analyses of the catheterization samples revealed a rise of blood oxygen content of 1.6 vol. % between the right atrium and right ventricle. This would indicate either a stream of arterial blood entering the right side of the heart at this level, or regurgitation of blood of a higher oxygen content from the pulmonary artery as, for example, in patency of the ductus arteriosus. The latter possibility is eliminated by the successive fall in oxygen values as the catheter is advanced along the pulmonary tree. This fall is probably due to better mixing of the shunted blood with the venous circulation in the distal portion of the pulmonary artery.

Evaluation of the magnitude of the left-to-right shunt involved in this case can be approximated through the use of special formulae devised by Ordway.[14]

$$\gamma = \frac{\overline{pa} - v}{a - \overline{pa}} = \frac{11.7 - 10.9}{16.2 - 11.7} = \frac{0.8}{4.5} = 0.18^{*} \text{ (Left-to-right shunt)}$$

$$\Lambda = \frac{a - v}{a - \overline{pa}} = \frac{16.2 - 10.9}{16.2 - 11.7} = \frac{5.3}{4.5} = 1.18 \text{ (Pulmonary blood flow relative to systemic blood flow)}$$

* Calculated on basis that systemic blood flow equals unity.

According to the Fick principle,

$$\text{Systemic blood flow} = \frac{\text{Oxygen uptake}}{\text{A-V difference}} = \frac{180}{5.3} = 3400 \text{ cc./min.}$$

$3400 \times 0.18 = 600$ cc./min. = Flow through shunt.

$3400 \times 1.18 = 4000$ cc./min. = Pulmonary blood flow.

Evaluation of the pressure records shows that slightly high pressures were obtained both in the greater and in the lesser circulations. The systemic elevation was assumed to be due to the excited physical and mental condition of the child at the time the tracing was taken. The elevation of pressure in the right ventricle and pulmonary artery may, however, be secondary to the increased volume of blood handled by the lesser circulation as a result of the blood shunted into the right ventricle.

Discussion

Aneurysms of the sinuses of Valsalva have excited interest and discussion because of their distinctive and unusual clinical manifestations since Thurnam's original definitive report. The characteristic train of events following the occurrence of rupture has been repeatedly described.[2, 7, 11, 15, 16] Onset is sudden and a sense of severe substernal oppression is common. Evidences of acute pulmonary congestion, such as dyspnea and orthopnea, are prominent. Physical examination reveals the sudden appearance in a previously normal heart of:

"A superficial harsh, and peculiarly intense sawing or blowing sound, accompanied by an equally marked purring tremor, heard over the varicose orifice, and in the current of the circulation beyond it; this sound is continuous, but is loudest during the systole, less loud during the diastole and still less so during the interval. The characters of this sound, as regards intensity and continuousness, will probably altogether distinguish it from any that is heard in ordinary cases of aneurism, or valvular disease of the heart."[1]

Murmur and thrill vary in location according to the point of rupture. The murmur has been variously described as "sawing," "buzzing," "purring" or "roaring," and has sometimes been recorded as systolic only.

Pallor and cyanosis are noted frequently at the time of rupture. Peripheral signs of aortic insufficiency, such as wide pulse pressure, collapsing pulse and capillary pulsation, develop if the blood flow through the aneurysmal fistula is sufficiently large.

Compensatory efforts on the part of the body result initially in an increase in the rate and force of the cardiac contractions and eventually in an increase in the total blood volume.[16] The output of the left ventricle is increased; the systemic systolic pressure rises but the diastolic remains low.

Maintenance of compensation depends primarily upon the magnitude of the shunt through the ruptured aneurysm, but is, in general, limited to a few weeks or months. After this time progressive and intractable failure leads rapidly to a fatal termination. An exception is reported by Abbott[2] in a case in which life continued for nine years after the time of rupture.

The present case is interesting from several viewpoints. First, this is believed to be the youngest patient with a ruptured aneurysm of a sinus of Valsalva of congenital etiology reported, and the only one in early childhood with the possible exception of Ramsey and Mosquera's case. Second, the benign course of the lesion following rupture is quite at variance with the usual clinical course. This may be explained in part by the apparently small size of the communication as determined by catheterization figures. The smallness of the shunt is further reflected by the absence of any of the usual peripheral signs of aortic insufficiency which so frequently are manifest following rupture and also

by the lack of increased prominence of the pulmonary vascular markings by fluoroscopy. Third, the apparent establishment of the diagnosis *in vivo,* while previously reported,[17] is nevertheless unusual.

It may be well to review the evidence in favor of the diagnosis at this point: 1. The clinical evidence is most convincing, *viz.,* history of sudden onset of signs of pulmonary congestion and cardiac failure with the simultaneous appearance of a continuous superficial murmur and thrill over the body of the heart. This murmur and thrill, though superficially similar to those of patent ductus arteriosus, were located far down over the body of the heart, an almost inconceivable location for the murmur of a patent ductus. 2. The figures at cardiac catheterization, while nonspecific and indicative only of a left-to-right shunt at the level of the right ventricle, do tentatively localize the point of rupture. A high interventricular septal defect, which is frequently a simultaneously occurring lesion in congenital sinus of Valsalva aneurysm,[2] would explain the catheterization figures. Against this possibility is the absence of evidence of cardiac abnormalities in the past, the type and location of the murmur, and the mother's statement that the precordial thrill appeared only after the presumed time of rupture.

Evidence that the aneurysm originated in the right sinus of Valsalva is conjectural only and depends upon the fact that the right sinus is most frequently involved and is the one most likely to give rise to an aneurysm rupturing into the right ventricle.

Finally it is interesting to speculate upon the prognosis in this case. Consideration of the catheterization figures reveals that only a small left-to-right shunt (18%) is present. This is of about the same order as that believed to be typical of the small, usually benign ventricular septal defect. It perhaps may be postulated that the prognosis in this case is equally good assuming no further increase in size of the fistulous tract takes place.

Summary

A case of aneurysm of a sinus of Valsalva, with rupture, in a four year old female child is presented. This is believed to be the youngest patient with rupture as yet reported.

Studies on the case undertaken in an attempt to verify the diagnosis *in vivo* included cardiac catheterization, which yielded results compatible with a stream of arterial blood entering the venous circulation at the level of the right ventricle; arterial oxygen analyses; and oxygen uptake determination. From figures obtained by these procedures the extent of the left-to-right shunt was calculated to be about 18% of the systemic blood flow. An attempt was made to correlate the unusually benign clinical course with the results obtained from these procedures.

Acknowledgments

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SPANISH ABSTRACT

Las Aneurismas del Sinus de Valsalva, con Reporte de un Caso

Se cree que este caso (niña de 4 años) de aneurisma del sinus de Valsalva, con ruptura, es el mas joven todavía informado en la literatura. La enfermedad empezó súbitamente con un "espasmo," dispnea, y ortopnea. El exámen físico mostró un soplo muy superficial y también un estremecimiento. Después de unos días los síntomas desaparecieron, los cuales, hasta la ultima visíta de la niña al hospital, no se han vuelto a repetir.

Mediante estudios, *in vivo,* incluyendo cateterismo del corazón y análisis del oxígeno arterial y de la absorción de oxígeno, se ha establecido que una corriente de sangre arterial entraba en la circulación venosa al nivel del ventrículo derecho. El tamaño del "shunt" se ha calculado alrededor de 18% de la corriente sistémica.

Ya que es posible que la historia se pueda explicar si es que existe un defecto del séptum interventricular, el soplo, el estremecimiento y la ausencia de síntomas y signos de esta enfermedad no conforman con dicha explicación.

El curso clínico, el cual ha sido leve, parece ser debido a un "shunt" relativamente pequeño.

Louisiana State University School of Medicine

ELECTROCARDIOGRAPHIC PATTERNS OF NORMAL CHILDREN FROM BIRTH TO FIVE YEARS OF AGE

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Chicago

IN A recent study from this institution, Switzer and Besoain[1] reported upon the normal limits of the electrocardiographic contour in children from 1½ to 15 years of age. Only seven of their patients were less than 5 years of age. The present study was undertaken to evaluate the electrocardiogram more completely in this younger age group, i.e., children ranging from birth to 5 years. This study therefore supplements the control series from this institution which can serve as a baseline for further studies.

The importance of such an evaluation is obvious and was recently stressed by Tudbury and Atkinson.[2] However; the present authors should like to re-emphasize the following:

1. The accurate interpretation of a child's ECG is no longer a matter of academic interest in view of the possibilities of cardiac surgery.

2. It has been noted by many observers[3-9] that the electrocardiographic patterns in normal children differ from those in adults especially as regards the contour of the entire QRS complex, the Q-waves and the direction of the T-waves in both limb leads and chest leads.

3. There are few published studies of the normal pattern of the ECG in the younger groups using the aV limb leads and the V chest leads from both the right and left sides.

In the present report two features not previously described are pointed out: namely, the involution of the right ventricular dominance in the chest leads and the variations in T-wave contour seen during the first weeks of life.

MATERIALS AND METHODS

A study was made of 130 ECGs of 104 normal infants and young children from a few hours to 5 yr. of age. The material was obtained (1) from the newborn nursery, (2) from the well baby and general pediatric clinics and (3) from the pediatric wards.

Forty-six of the cases were males and 58 were females. Table 1 indicates the distribution of material by age and sex.

The newborn infants were considered normal by physical examinations. The normality of the patients from the well baby clinic was assured by more thorough and prolonged follow-ups.

The cases from the pediatric clinic were obtained at random from the daily attendance. They were either patients with minor complaints or healthy children brought by their parents to the clinic in company with sick siblings. The cases obtained from the wards consisted either of noncardiac cases ready for discharge or patients presenting no evidence of disease associated with or capable of producing cardiac impairment.

ECGs were taken with a Sanborn Cardiette, the patients being in the recumbent position. Special children's electrodes measuring 1.5 cm. in diameter were used. The routine ECGs consisted of the following 12 leads: the 3 standard limb leads, aV limb leads and chest leads V4R, V1, V2, V4, V5 and V6.

Measurements were made in every tracing of heart rate and rhythm, "electric" position, P-wave

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TABLE 1

AGE AND SEX DISTRIBUTION

	Male	Female	Total
Under 1 wk.	13	21	34 Cases (60 Records)
1 wk. to 3 mo.	3	6	9
3 to 6 mo.	10	8	18
6 mo. to 1 yr.	1	5	6
1 to 2 yr.	9	5	14
2 to 3 yr.	2	7	9
3 to 4 yr.	4	4	8
4 to 5 yr.	4	2	6
Total	46	58	104 Cases (130 Records)

direction, duration and amplitude, P-R interval, QRS duration, and the amplitude of each of its components, T-wave direction, duration and amplitude, S-T deviation, R/S, R/T and Q/R ratios, and location of the QRS transition zone over the precordium.

The tracings were grouped, according to table 1, in 8 groups. For simplification, however, these age groups were condensed or separated according to the needs of various aspects of this presentation.

RESULTS

Rhythm: The results are recorded in table 2. Sinus arrhythmia was more frequently encountered in the older age groups, where the rate was slower.

TABLE 2

HEART RATE (PER MIN.) AND RHYTHM

	80 or less	81 to 100	101 to 121	121 or more	Sinus Rhythm	Sinus Arrhythmia
Birth to 1 yr.	0	6	14	47	56	11
1 to 5 yr.	0	16	12	9	19	18

TABLE 3

"ELECTRIC" POSITION

	Vertical	Semivertical	Intermediate	Semihorizontal	Horizontal
Birth to 1 wk.	32	1	0	0	1
1 wk. to 3 mo.	1	3	2	1	2
3 to 6 mo.	3	9	1	0	5
6 mo. to 1 yr.	4	0	2	0	0
1 to 2 yr.	11	0	1	0	1*
2 to 3 yr.	8	0	0	0	0*
3 to 4 yr.	8	0	0	0	0
4 to 5 yr.	6	0	0	0	0
Total	73	13	6	1	9=102

* One case of "indeterminate" position.

"Electric" position: Table 3 indicates the "electric" position in the several age groups. The vertical and semivertical positions were the most frequently encountered.

P-Wave: The results are presented in tables 4 and 5. From the data presented it appears that there is a similar pattern for P-waves in all the groups.

TABLE 4

HEIGHT OF P-WAVE (mm.)

	Birth to 1 wk.				1 wk. to 3 mo.				3 mo. to 1 yr.				1 to 5 yr.			
Lead	Max.	Min.	Av.	Usual	Max.	Min.	Av.	Usual	Max.	Min.	Av.	Usual	Max.	Min.	Av.	Usual
1	+1	+0.5	+0.8	+	+1	+0.5	+0.8	+	+1	+0.25	+0.6	+	+1	+Tiny	+0.5	+
2	+3	+1	+2.0	+	+1	+0.50	+0.75	+	+2	+Tiny	+1.0	+	+1.5	+0.25	+1.0	+
3	+2	+0.25	+1.0	+	+Tiny	−1	Ind.	+	+1	−Tiny	+0.3	+	+0.75	Ind.	+0.3	+
R	−1.5	−0.5	−1.0	−	−1.5	−0.50	−1	−	−2	−0.50	−0.9	−	−1	−Tiny	−0.6	−
L	+0.75	Ind.	+0.3	+	+1.5	+0.25	+0.4	+	+0.50	Ind.	+0.2	+	+0.25	−Tiny	+0.1	+
F	+2	+0.25	+1.1	+	+1	+Tiny	+0.5	+	+1.50	−0.25	+0.5	+	+2	+0.25	+0.5	+
V_4R	+1	−0.25	+0.5	+	−1.50	−0.25	−0.4	−	+1	−Tiny	+0.1	+	+1	Ind.	+0.1	+
V_1	+2	−Tiny	+1.1	+	+1	Ind.	+0.5	+	+2	−Tiny	+0.1	+	+1.25	−Tiny	+0.4	+
V_2	+1.5	+0.25	+1.1	+	+1	+Tiny	+0.5	+	+2	+0.25	+0.5	+	+1	−0.25	+0.5	+
V_4	+1.5	+0.50	+1.0	+	+1	+0.25	+0.6	+	+1	Ind.	+0.3	+	+1	+Tiny	+0.3	+
V_5	+1	+0.50	+0.4	+	+1	+0.50	+0.7	+	+1	Ind.	+0.4	+	+1	+Tiny	+0.2	+
V_6	+1.5	Ind.	+0.5	+	+1	+0.25	+0.4	+	+0.50	Ind.	+0.2	+	+1	Ind.	+0.2	+

+ = Upright.
− = Inverted.
Ind. = Indiscernible.

TABLE 5

DURATION OF P-WAVE (sec.)

Lead	Birth—1 wk.			1 wk.—3 mo.			3 mo.—1 yr.			1—5 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	0.05	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
2	0.06	0.04	0.04	0.06	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
3	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06
R	0.04	0.04	0.04	0.06	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
L	0.04	0.04	0.04	0.06	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06
F	0.07	0.04	0.05	0.04	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
V_4R	0.04	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
V_1	0.06	0.04	0.05	0.04	0.04	0.04	0.06	0.04	0.05	0.08	0.04	0.06
V_2	0.06	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
V_4	0.08	0.04	0.05	0.04	0.04	0.04	0.08	0.04	0.06	0.08	0.04	0.06
V_5	0.08	0.04	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06
V_6	0.06	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.08	0.04	0.06

1. P is usually positive in 1, 2, aVF, V4, V5 and V6.
2. P is usually negative, but may occasionally be diphasic, in 3 and aVR.
3. P may be positive, negative or diphasic in 3, aVL, V4R, V1 and V2.

The P-wave amplitude never exceeded +3.0 mm. or −2.0 mm. Its duration increased with age. In no instance did any P-wave exceed 0.08 sec. nor were any less than 0.04 sec.

P is taller during the first week of life than later and its amplitude is usually greatest

in lead 2. The mean amplitude of P found is in accord with that given by Tudbury and Atkinson[2] and also Hafkesbring, Drawe and Ashman.[11]

P-R Interval: The data on P-R interval variations are tabulated in table 6. The P-R interval varies little from lead to lead. Before the age of 1 year, the P-R interval varies

TABLE 6

DURATION OF PR INTERVALS (sec.)

Lead	Birth—1 wk.			1 wk.—3 mo.			3 mo.—1 yr.			1 yr.—5 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	0.16	0.10	0.12	0.12	0.10	0.11	0.14	0.10	0.12	0.14	0.10	0.12
2	0.16	0.10	0.12	0.12	0.10	0.10	0.14	0.10	0.12	0.16	0.10	0.13
3	0.16	0.10	0.12	0.12	0.10	0.10	0.14	0.10	0.12	0.16	0.10	0.13
R	0.16	0.10	0.12	0.12	0.10	0.11	0.14	0.10	0.12	0.14	0.10	0.13
L	0.12	0.10	0.11	0.12	0.10	0.10	0.14	0.10	0.12	0.16	0.10	0.13
F	0.16	0.10	0.12	0.12	0.10	0.11	0.14	0.10	0.12	0.16	0.10	0.13
V_4R	0.16	0.10	0.12	0.12	0.10	0.11	0.14	0.10	0.12	0.16	0.12	0.13
V_1	0.16	0.10	0.12	0.12	0.12	0.12	0.14	0.10	0.12	0.16	0.12	0.13
V_2	0.16	0.10	0.12	0.12	0.12	0.12	0.14	0.10	0.12	0.16	0.12	0.13
V_4	0.16	0.10	0.11	0.12	0.10	0.11	0.14	0.10	0.12	0.16	0.12	0.13
V_5	0.16	0.10	0.11	0.12	0.10	0.11	0.14	0.10	0.12	0.16	0.12	0.13
V_6	0.12	0.10	0.11	0.12	0.10	0.11	0.14	0.10	0.12	0.16	0.12	0.13

TABLE 7

DURATION OF QRS COMPLEX (sec.)

Lead	Birth—1 wk.			1 wk.—3 mo.			3 mo.—1 yr.			1—5 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
2	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
3	0.04	0.04	0.04	0.04	0.04	0.04	0.06	0.04	0.04	0.06	0.04	0.05
R	0.04	0.04	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.04	0.04	0.04
L	0.04	0.04	0.04	0.04	0.03	0.04	0.06	0.04	0.05	0.06	0.04	0.05
F	0.04	0.04	0.04	0.04	0.03	0.04	0.06	0.04	0.05	0.04	0.04	0.04
V_4R	0.04	0.04	0.04	0.04	0.03	0.04	0.04	0.04	0.04	0.07	0.04	0.05
V_1	0.06	0.04	0.05	0.06	0.04	0.04	0.06	0.04	0.05	0.08	0.04	0.06
V_2	0.08	0.04	0.05	0.06	0.04	0.04	0.06	0.04	0.05	0.08	0.04	0.06
V_4	0.06	0.04	0.05	0.04	0.04	0.04	0.06	0.04	0.05	0.06	0.04	0.05
V_5	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.06	0.04	0.05
V_6	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04

from 0.10 to 0.16 sec. with an average of 0.12 sec. After that there is a tendency for it to lengthen. However, no P-R interval greater than 0.16 sec. was seen.

Duration of QRS Interval: The duration of the QRS complex (table 7) was fairly constant and averaged 0.04 sec. in most leads, the exceptions being V1, V2 and V4 where it was longer. The QRS duration, however, never exceeded 0.08 sec. The QRS duration found is shorter than that reported by Groedel and Miller[5] with CR leads; they reported a QRS duration of 0.06 sec. at four months.

Q Wave: The findings are given in table 8. In the first week of life, Q is absent in lead 1 and all chest leads (V4R to V6) but is often present in aVR, aVF and 3. After this age group, a Q wave is seen rather uniformly, in lead 3, aVR, aVF, V5 and V6 but is absent in lead 1, V4R, V1, V2 and V4. These findings are in contrast to those of Tudbury and Atkinson and in agreement with those of Seham and Moss,[12] who reported that

TABLE 8

DEPTH OF Q WAVE (mm.)

Lead	Birth—1 wk.			1 wk.—3 mo.			3—6 mo.			6 mo.—1 yr.		
	Max.	Min.	Usual	Max.	Min.	Usual	Max.	Min.	Usual	Max.	Min.	Usual
1	0	0	0	1.5	0	0	0.25	0	0	0	0	0
2	2	0	+	1	0	0	1	0	0+	1.5	0	0
3	1.5	0	+	5	0	+	4	0	+	4	0	+
R	3	0	+	11	0	+	13	0	+	10	0	+
L	3	0	0	1	0	0	3	0	0	0	0	0
F	2	0	+	1.5	0	+	3	0	+	2.5	0	+
V_4R	0	0	0	0	0	0	0	0	0	0	0	0
V_1	0	0	0	6	0	0	0	0	0	0	0	0
V_2	0	0	0	12	0	0	0	0	0	0	0	0
V_4	0	0	0	2	0	0	1	0	0	0	0	0
V_5	0	0	0	1.5	0	+	1	0	+	0	0	0
V_6	0	0	0	0.5	0	+	1	0	+	0	0	0

	1–2 yr.			2–3 yr.			3–4 yr.			4–5 yr.		
	Max.	Min.	Usual	Max.	Min.	Usual	Max.	Min.	Usual	Max.	Min.	Usual
1	2.5	0	0	0.5	0	0	2	0	0	0.25	0	0
2	1.5	0	+	1	0	+	3	0	+	0.25	0	0
3	3	0	+	1.5	0	+	1.5	0	+	1	0	+
R	12	0	+	8	0	+	11	0	+	11	7	+
L	5	0	0	4	0	0	1.1	0	0+	1	0	+
F	1.5	0	+	1.5	0	+	2.5	0	+	0.25	0	0
V_4R	4	0	0	3	0	0	0	0	0	0	0	0
V_1	1	0	0	0	0	0	0	0	0	0	0	0
V_2	1.5	0	0	0	0	0	0	0	0	0	0	0
V_4	2	0	0	0	0	0	5	0	0	0.5	0	0
V_5	4	0	+	1	0	+	3	0	+	1	0	+
V_6	3	0	+	1	0	+	3	0	+	1	0.5	+

0=absent.
+=present.

Q was totally absent during the first month of life in lead 1. As a matter of fact, with a few exceptions Q was found absent up to 3 years of age. Q did not exceed 25% of the R wave in any lead except in aVR where it dominates the ventricular complex.

R-Wave: A correct evaluation of the R-wave in the chest leads and the aV limb leads, especially aVR, V4R and V1, is of great importance in the younger age groups since an entirely upright ventricular complex or an RS in the right sided chest leads could be considered evidence of right ventricular strain or hypertrophy, if criteria developed for the ECG of the adult be applied. An M-shaped or polyphasic QRS complex or slurring of

the limbs of the R-wave was a frequent finding especially in the transition zone. These are considered normal findings.

The height of the R-waves and the R/S ratios in the different leads are presented in tables 9 and 10.

S-Wave: As expected with a predominance of the vertical and semivertical positions,

TABLE 9

HEIGHT OF R-WAVE (mm.)

Lead	Birth—1 wk.			1 wk.–3 mo.			3–6 mo.			6 mo.–1 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	4	0	1.2	9	4	6.4	11	5	7.8	8	4	6.3
2	10	T	4.5	11	3	7.3	13	5	9.2	12	7	10.0
3	12	T	6.3	7	0	3.0	10	0.25	5.2	9	4	6.7
R	7	T	4.2	3	0	1.8	3	0	1.3	7	0.5	3.0
L	3	0	1.6	8	2	4.5	9	2	4.7	7	2	4.7
F	13	T	5.4	10	2	5.2	9	T	5.9	11	5	8.0
V_4R	14	2.5	5.3	5	0.5	3.0	7	0.5	3.1	8	1	4.0
V_1	11	5	8.0	13	7	10.3	12	5	7.6	10	5	7.0
V_2	15	6	9.5	16	12	13.1	20	11	13.4	15	8	11.7
V_4	12	1.5	7.0	15	6	12.3	19	10	13.5	15	9	12.6
V_5	7	2	3.0	1.5	5	12.5	17	7	12.0	12	8	10.6
V_6	3.5	1	2.0	14	2	9.5	11	4	7.9	7	6	6.3
	1–2 yr.			2–3 yr.			3–4 yr.			4–5 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	10	2.5	7.0	7	1	4.0	5	3	4.7	7	5	6 0
2	18	2	11.6	14	4.5	8.9	13	8	9.7	14	7	8.7
3	10	T	8.0	12	1.5	6.6	8	3	6.0	13	0.25	4.3
R	2.5	0	0.7	1.5	T	0.5	2	0	0.7	1.5	0	0.8
L	5	0	4.1	3.5	0.25	1.5	2.5	1	1.8	4	1	2.3
F	14	1.5	9.8	12	3.5	7.5	10	5	7.3	15	8	9.3
V_4R	10	1	3.7	3	0.5	2.4	5	1	2.8	4	2	2.2
V_1	11	3	7.5	10	2.5	5.9	8	T	5.2	9	3	5.7
V_2	20	6	13.2	16	5	11.6	15	9	12.7	10	6	8.0
V_4	17	8	13.5	10	5	8.6	18	10	13.0	20	15	17.0
V_5	17	7	12.5	11	4	7.6	13	8	11.0	19	13	13.5
V_6	15	4	8.4	8	4	7.5	12	8	10.0	15	9	9.3

0=absent.
T=less than 0.5.

a deep S-wave was almost invariably present in lead 1 during the first week of life. From 1 week until 5 years of age, the S-wave tended to become smaller in lead 1 and a deep S-wave is often encountered in lead 3. The evolution of the S-wave in the chest leads, especially the right-sided ones (V4R, V1 and V2) is inversely parallel to the involution of the R-waves as the left ventricular dominance appears in the ECGs of the older age groups. Fairly deep S-waves may be present in V5 and V6 during the first few months of life. The depth of the S-waves in all leads is charted in table 11.

Transition Zone of QRS: The transition zone was studied according to the criteria of Wilson:[10]

From birth to 1 week the transition zone is usually between V1 and V2.

From 1 week to 3 months no real transition zone was found.

From 3 months to 1 year the transition zone usually occurs in V2.

TABLE 10

R/S RATIO

Lead	Birth—1 wk.			1 wk.—3 mo.			3—6 mo.			6 mo.—1 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	0.4	0.1	0.2	6	1.5	4.8	20	1.4	5.7	3.5	1	2.4
2	∞	0.8	1.3	∞	0.6	8.3	∞	3	6.0	∞	1.7	2.6
3	∞	3.3	1.4	∞	0.3	0.5	∞	1.1	3.0	∞	4	4.3
R	∞	0.5	4.5	∞	1.6	1.8	∞	0	0.3	∞	0.1	1.0
L	0.3	0.1	0.1	16	0.5	8.0	28	0.5	6.3	2.0	0.8	1.3
F	∞	1.3	3.0	∞	0.4	7.1	∞	2.5	4.3	∞	2.7	3.8
V_4R	13.0	1.5	8.2	∞	2.7	2.8	2.0	0.16	0.8	4.0	2.0	3.0
V_1	2.3	0.9	1.4	6.5	1.8	3.7	4.0	0.9	1.7	2.5	1.2	1.7
V_2	4.6	0.8	1.7	6.5	1.1	2.4	1.4	1.0	1.2	2.0	1.0	1.7
V_4	1.0	0.1	5.0	6.5	1.3	3.8	1.7	0.8	1.4	2.8	1.3	2.1
V_5	1.0	0.3	6.0	13.5	1.0	8.0	4.3	1.0	2.8	4.0	1.7	2.9
V_6	0.7	0.3	5.0	∞	1.8	7.7	22	1.0	14.0	6.0	1.5	3.3
	1–2 yr.			2–3 yr.			3–4 yr.			4–5 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	∞	5	1.2	∞	1.3	1.4	∞	5	5.0	28	3	12.0
2	∞	2.5	7.2	∞	1.7	5.5	∞	8.76	23.3	∞	5	7.0
3	∞	0.7	7.0	∞	2.8	7.3	∞	16	24.0	22	0.5	9.8
R	0.14	0	0.08	∞	0.0	0.2	0.28	0	0.1	∞	0	0.3
L	∞	1	2.6	∞	0.4	1.5	∞	0.5	1.3	8	0.5	3.1
F	∞	0.57	14.5	∞	4.4	5.9	∞	10	23.0	∞	7.3	11.7
V_4R	∞	0.62	8.8	∞	0.5	0.9	5	0.5	2.4	0.7	0.5	0.6
V_1	∞	0.75	20.2	2.4	0.3	1.1	1.6	0.3	1.0	0.8	0.5	0.6
V_2	∞	0.90	8.0	3	0.8	1.4	1.5	0.8	1.0	5.5	0.5	1.9
V_4	∞	2.14	2.6	3.7	1.0	1.6	∞	2	4.0	5.3	3.3	4.6
V_5	∞	3.14	6.3	16	1.3	6.0	∞	10	11.5	8.7	7.0	7.8
V_6	∞	4	8.1	∞	3.0	7.9	∞	24	32.0	∞	6.7	12.3

∞ = Infinity.

From 1 to 2 years the transition zone is broad, appearing in several leads between V1 and V5.

From 2 to 3 years years the transition zone is between V2 and V4.

From 3 to 5 years the transition zone is between V2 and V3.

T-Waves: In children less than 24 hours old, several instances of upright and diphasic T-waves in V4R, V1 and V2 and inverted T-waves in V5 and V6 were encountered. Since these findings were not present in 3 and 4 day old infants an evaluation of T-wave progression during the first few days of life was deemed desirable.

Ten additional cases were selected from the newborn nursery for special analysis and ECGs were taken the day of birth and every day thereafter up to the fourth day (Fig. 1).

In the first 24 hours of life, T is upright or diphasic in V4R, V1 and V2 and inverted in V4, V5 and V6. Thereafter, there was a gradual reversal of the T-wave direction so

TABLE 11

DEPTH OF S-WAVE (mm.)

Lead	Birth—1 wk.			1 wk.—3 mo.			3—6 mo.			6 mo.—1 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	8	3.5	5.0	4	0	1.6	6	0	3.0	8	1.5	6.5
2	6	0	3.5	5	0	1.4	3	0	0.95	7	0	3.0
3	3	0	1.0	10	0	2.1	6	0	1.0	2	0	3.3
R	2	0	1.0	6	0	1.4	13	0	4.3	9	0	3.0
L	9	3.5	5.1	2	0.25	1.0	7	0	3.9	6	1	4.0
F	4	0	2.0	6	0	1.2	2	0	0.5	3	0	1.3
V_4R	2	0	0.1	1.5	0	0.9	7	0.5	2.8	2	0.5	1.2
V_1	10	3	5.5	6	0	2.1	11	2	6.1	5	2	4.0
V_2	15	7	11.4	10	0	6.5	20	8	11.6	15	4	8.3
V_4	14	11	13.0	7	2	4.3	15	2	8.5	12	4	7.0
V_5	8	3	5.5	8	1	2.6	9	1	4.4	7	2	4.4
V_6	7.5	3	4.3	5	0	1.4	7	0	1.8	4	1	2.7
	1–2 yr.			2–3 yr.			3–4 yr.			4–5 yr.		
	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Av.
1	4	0	1.5	2	0	0.6	1	0	0.6	2.5	1	1.1
2	2	0	0.6	3	0	1.4	1.5	0	0.6	2	0	1.0
3	8.5	0	0.8	2.5	0	0.9	0.5	0	0.3	8	0	0.6
R	12	0	7.7	11	0	6.0	11	6	8.0	8	0	2.6
L	5	0	2.5	4	0	2.8	2	0	1.0	3	0.5	1.8
F	7	0	0.8	2.5	0	1.0	1	0	0.3	1.5	0	0.7
V_4R	7	0	3.6	10	0	4.2	4	1	2.3	4	3.5	3.8
V_1	17	0	6.8	16	2.5	9.9	9	3	5.7	11	5	8.7
V_2	19	4.5	11.6	17	4	14.0	16	10	12.7	16	11	13.0
V_4	7	0	3.4	8	3	5.6	5	0	2.7	6	3	4.0
V_5	4	0	1.6	3	0.5	1.6	1	0	0.7	2	1.5	1.8
V_6	1.5	0	0.8	2	0	0.8	0.5	0	0.2	1.5	0	0.7

0=absent.

that at the fourth day all cases had inverted T-waves in V4R, V1 and V2 and upright T-waves in V5 and V6. Thus, T-wave inversion in the right-sided chest leads in children appears only after the first few days of life.

After the first week of life the T-wave presents a rather uniform pattern in the entire series. T is usually upright in the standard limb leads aVL, aVF, V4, V5 and V6; and usually inverted in aVR, V4R, V1 and V2 (table 12).

S-T Segment: The S-T junction was nondeviated in all cases. The S-T segment usually sloped upwards or downwards to merge with the first limb of the T-wave. There was no bowing or coving in a direction opposite the T-wave.

Discussion

The ECG in children under the age of 5 years varies from the pattern present at birth until the adult pattern is almost completely attained. A striking finding in newborn infants during their first week of life is a completely upright ventricular complex or an RS in all chest leads. This pattern is a normal finding. It goes through a regular involution as the left ventricle becomes more and more dominant. An attempt was made to determine the exact time for this involuting process of the right ventricular dominance, in order to

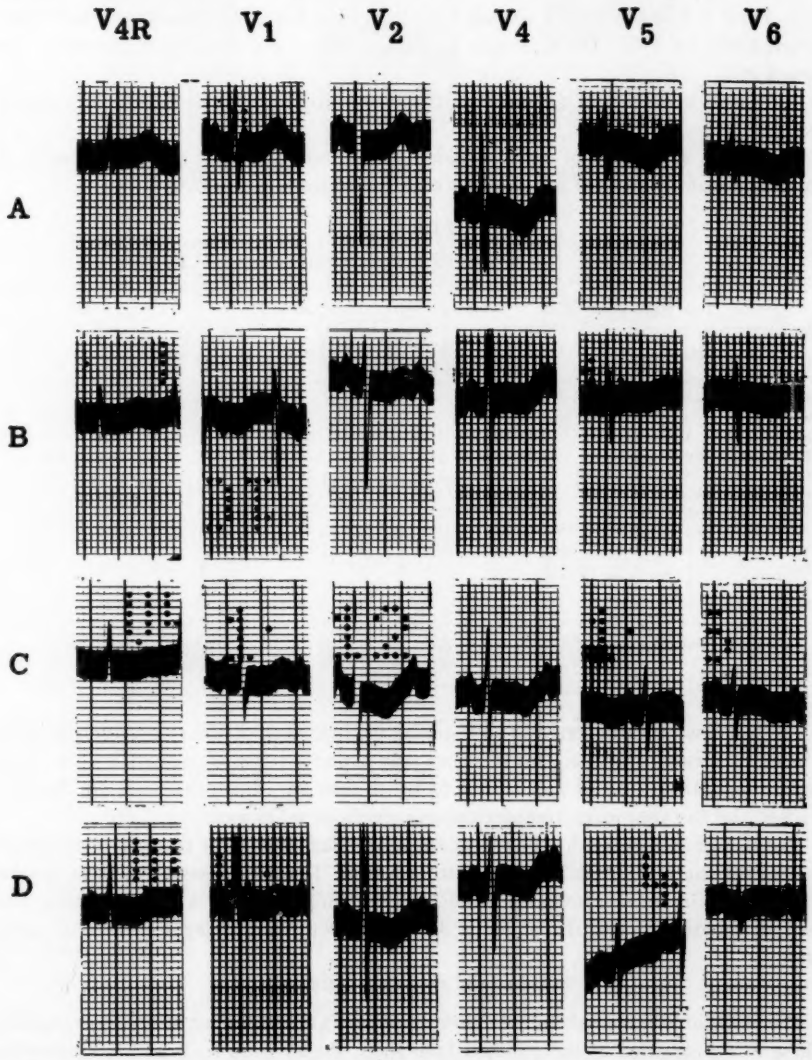

Fig. 1. Chest leads from normal child at various periods after birth. A. 3 hr. after birth; B. 27 hr.; C. 51 hr; D. 75 hr. (See discussion of figure in text.)

be able to distinguish the normal tall R-wave from that of the true right ventricular strain seen with congenital heart disease. Thus it is evident that it may be extremely difficult to diagnose right heart strain in a child under 3 years of age, from just one tracing. It is the progression that it is important.

From the authors' study the following conclusions can be drawn (Fig. 2):

1. During the first 12 weeks of life, aVR shows normally a tall R-wave and V4R consists of an R-wave occasionally followed by a tiny S-wave. In V4R the R/S ratio is greater than 1 and approaches infinity.

2. From 3 months up to 1 year of age, the R- and S-waves tend to equal each other progressively in V4R. The R/S ratio is greater than 1 but tends progressively to approach it.

3. From 1 to 3 years of age, the R- and S-waves tend to be equal and the R/S ratio is usually 1.

4. From 3 to 5 years of age and older, the R-wave is usually definitely smaller in amplitude than the S-wave and the R/S ratio consequently is less than 1.

TABLE 12

HEIGHT OF T-WAVE (mm.)

Lead	1 wk.–3 mo.				3–6 mo.				6 mo.–1 yr.				1–5 yr.			
	Max.	Min.	Av.	Usual	Max.	Min.	Av.	Usual	Max.	Min.	Av.	Usual	Max.	Min.	Av.	Usual
1	3	−0.5	1.4	+	3	1	1.6	+	2	0.5	1.5	+	4	0.5	1.7	+
2	3	0.5	1.6	+	3	1	1.9	+	4	1	2.5	+	4	0.5	2.9	+
3	1	T	0.1	+	3	−0.3	1	+	2.5	−0.5	0.5	+	3	Ind.	0.9	+
R	−2	−0.5	−1	−	−3	−1	−2	−	−3	−0.5	−1.8	−	−4	−1	−2.6	−
L	2.5	T	0.9	+	3	Ind.	1.1	+	0.3	Ind.	0.2	+	2	Ind.	0.3	+
F	3	Ind.	0.8	+	2	0.5	1.2	+	4	Ind.	2.5	+	3	Ind.	2.3	+
V_4R	−2	−0.5	−1.1	−	−4	−1	−2.1	−	−2	−0.5	−1.1	−	−3	Ind.	−1.6	−
V_1	−4	−1	−1.6	−	−5	−1	−3.0	−	−3	−1	−2.1	−	−4	−1	−2.7	−
V_2	−4	−0.5	−1.2	−	−4	−1	−3.0	−	−4	−2.5	−3.2	−	−5	−1.2	−2.7	−
V_3	6	2	2.2	+	3	−1	1.8	+	2	1.5	1.7	+	5	−1.5	2.6	+
V_5	5	2	1	+	5	1	2.3	+	3	0.5	1.8	+	4.5	0.5	2.6	+
V_6	4	1	1.6	+	5	1	2.2	+	2	0.5	1.3	+	3.5	0.5	2.5	+

Ind. = Indiscernible.
T = Tiny.
+ = Upright.
− = Inverted.

The tall R-wave encountered in aVR during the first week of life recedes greatly from 1 week to 3 months of age. However, one may expect a rather significant R-wave to be present until 18 months of age in aVR, at which time the adult pattern has usually been reached and the ventricular complex consists chiefly of a QS wave.

The change in T-wave direction in the first 48 hours after birth remains unexplained. In a recent study of the ECGs of premature infants, Thaon[13] suggests that there may be a disturbance in the repolarization process in these infants. If this is so it is possible that the repolarization process is changed at birth along with other changes in the fetal circulation.

SUMMARY AND CONCLUSIONS

The ECGs of 104 normal children from a few hours old to 5 years of age were studied. These ECGs consisted of the standard limb leads, the aV limb leads and six precordial leads: V4R, V1, V2, V4, V5 and V6.

While the number of cases in each group are small, the following conclusions are suggested by this study:

1. ECGs of the newborn infant present important variations from those seen in later life. This is especially true during the first week of life. Thereafter the contour evolves

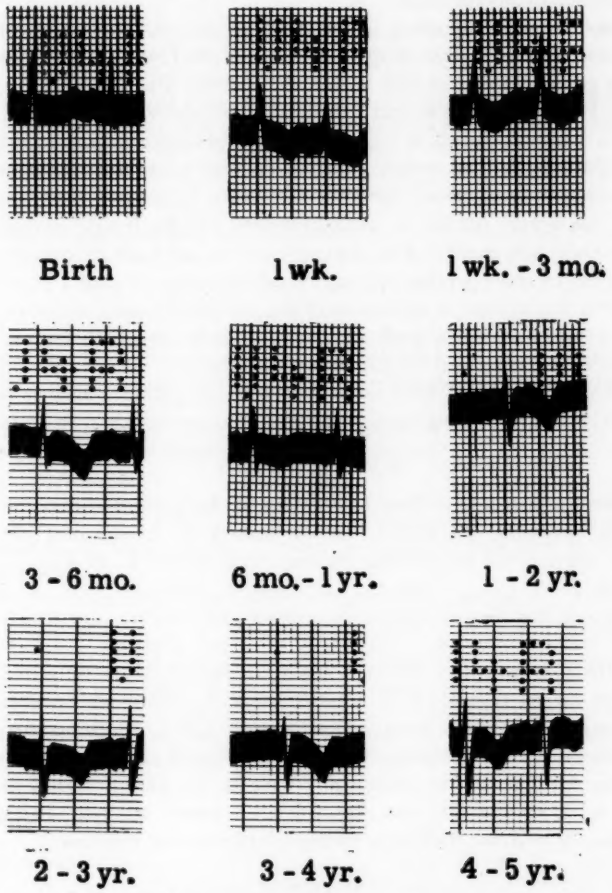

FIG. 2. Evolution in appearance of normal V4R during 1st 5 yr. of life.
(See discussion of figure in text.)

in a definite manner until the adult-like pattern is reached.

2. The vertical and semivertical "electric" positions were the most frequently encountered in this age group.

3. P-waves present a rather permanent pattern in this age range:
   a. is usually upright in lead 1 and 2, aVF, V4, V5 and V6.
   b. is usually inverted in lead 2 and aVR.
   c. is either upright, inverted or diphasic in lead 3, aVL, V4R, V1 and V2.

4. The P-R interval varies from 0.10 sec. minimum to 0.16 sec. maximum with the

average being 0.12 sec. in this age range. It tends to become greater in the older age groups.

5. QRS duration is shorter in the younger age groups and increases slowly with age.

6. Polyphasic, M-shaped or slurred QRS complexes are not uncommon in the ECGs of normal children in this age range.

7. A Q wave is frequently absent in lead 1 and in all chest leads during the first week of life. Thereafter up to 5 years of age the pattern of the Q wave is as follows:

a. Q is generally absent in lead 1, V4R, V1, V2 and V4.

b. Q is generally present in lead 3, V4R, aVF, V5 and V6.

8. There is a distinct pattern of right ventricular dominance in leads from the sternum and to its right at birth. This pattern gradually undergoes involution, probably related to normal physiologic development, until the left ventricle becomes dominant. Thus the evolution of the S-wave parallels a gradual involution of the R-wave in right precordial leads and probably also in aVR. This dominance of the left ventricle over the entire precordium is usual by about 3 years, but may be delayed normally until 5 years of age.

9. The T-wave is upright or diphasic in V4R, V1, and V2 and inverted in V5 and V6 for the first 24 hours of life; it gradually alters so that by the fourth day it is inverted in V4R, V1 and V2 and upright in V5 and V6 and thereafter.

10. The transition zone of QRS varies from one age group to another and tends in some ages to be broad. In some instances no real transition zone can be determined.

Acknowledgment

The authors are indebted to Drs. L. N. Katz, R. Langendorf and A. Pick for their suggestions in preparing this report. The cooperation of the attending physicians and house staff is appreciated; in particular the cooperation of Dr. B. M. Kagan is gratefully acknowledged.

Addendum

Some of the presented data (point 8 and 9 of summary) are fully confirmed by a recent study of Ziegler (Ziegler, R. F., Characteristics of unipolar precordial electrocardiogram in normal infants, Circulation **3**:439 (March) 1951), which appeared after this paper was submitted for publication. The article of Kuskin and Brockman (Kuskin, L., and Brockman, L., Direction of precordial T-wave in 321 normal infants and children, Am. J. M. Sc. **218**:65, 1949) was drawn to the authors' attention. Part of the preceding summary is in accord with these findings of Kuskin and Brockman.

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SPANISH ABSTRACT

Caracteristicas Electracardiograficas de Niños Normales Desde el Nacimiento Hasta los Cinco Años de Edad

El estudio de 130 electrocardiogramas obtenidos en 102 niños, divididos en ocho grupos entre el nacimiento y cinco años de edad, sugirió las siguientes conclusiones:

1. Los electrocardiogramas de los recién nacidos presentan variaciones importantes de las observadas mas tarde en la vida. Esto es especialmente notable durante la primera semana de nacido. Después, el contorno del electrocardiograma se desenvuelve de una manera definitiva hasta alcanzar las caracteristicas del adulto.

2. Las posiciones "electricas" verticales y semiverticales fueron las mas frecuentemente encontradas en este grupo. Las variaciones normales del intervalo P-R osciló entre 0.10 y 0.16 segundos y para el QRS de 0.04 y 0.08 segundos.

3. La onda Q está frecuentemente ausente en desviacion I, y en todas las desviaciones precordiales durante la primera semana de nacido. Después, la onda Q está generalmente ausente en desviacion I, y en las desviaciones precordiales derecha, y presente en desviaciones III, aVF en las desviaciones precordiales izquierdas.

4. Se observó en las desviaciones precordiales, un cambio gradual de las caracteristicas de preponderancia fisiologica del ventriculo derecho presentes al nacimiento, hacia la preponderancia del ventriculo izquierdo, desarrollada después de los cinco años de edad. Una onda R prominente, normalmente presente al nacimiento en V1 y V2, se reduce gradualmente con la edad y con el desarrollo de la onda S. Cambios similares fueron observados en aVR.

5. La onda T es positiva o difásica en las desviaciones precordiales derechas y negativa en las desviaciones precordiales izquierdas durante las primeras 24 horas de nacido, y gradualmente se altera de forma que para el curato día de nacido en adelante es negativa en V4R, V1, y V2 y positiva en V5 y V6.

29th and Ellis Avenue

STUDIES ON THE ABSORPTION AND DISTRIBUTION OF CHLORAMPHENICOL

By RICHARD S. KELLY, M.D., ANDREW D. HUNT, JR., M.D.,
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CHLORAMPHENICOL has been demonstrated to be quickly and readily absorbed from the gastrointestinal tract. Ley et al.[1] have shown peak serum levels to be obtained two hours after ingestion of doses of 1.0 and 2.0 gm. in adults. With the smaller dose, the peak serum levels ranged from 5 to 15 μg./cc. and detectable levels were maintained for eight hours; the larger dose gave peak serum levels ranging from 20 to 30 μg./cc. and detectable levels were maintained for as long as 20 hours. Data showing roughly proportional increases in peak serum levels with increasing dosage from 0.5 to 2.0 gm. have been presented by Hewitt and Williams.[2] However, similar data have not yet been collected for infants and children. This study has been conducted with a view to making out a dosage schedule for pediatric purposes.

METHODS

Body fluid chloramphenicol levels were measured by means of a modification of the Osgood turbidimetric method.[3] By this method, determinations of known concentrations of chloramphenicol resulted in values deviating from the actual levels as follows: for human serum, 0 to 42%, with a mean of 13%, for spinal fluid 0 to 60%, with a mean of 24%. The least detectable level is 1 μg./cc.

Subjects were convalescent infants and children, well hydrated and with no clinical evidence of renal or cardiac disease. In single dosage studies, the antibiotic was given by one of the authors, either in capsule form for older children, or mixed in corn syrup for infants and younger children. The drug was given 2 hr. postprandially.

RESULTS

Since an effective single dose of aureomycin has been found to be 11 mg./kg.,[4] this amount was selected for the first trial with chloramphenicol. In three subjects detectable blood levels failed to appear.

Twenty-two mg./kg. were given to 12 subjects with the results shown in table 1. Peak serum levels were achieved, in most cases, two hours after ingestion. Serum levels at two hours ranged from 2.6 to 14.0 μg./cc. serum, with a mean value of 8.3 μg./cc. Six hours after ingestion of chloramphenicol, levels ranged from 2 to 6.4 μg./cc. with a mean value of 5 μg./cc. Detectable levels were still present at 10 hours.

Forty-four mg./kg. body weight were given to nine subjects, as shown in table 2. The range of two hour serum levels was 7 to 40 μg./cc. with a mean of 22 μg./cc. After six

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Chloramphenicol for this study was kindly supplied by Parke, Davis & Company.

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hours serum levels ranged from 3.6 to 17.8 μg./cc. with a mean of 10.4 μg/cc. Some of these values are plotted in chart 1.

It will be noted that in an occasional patient peak serum levels were attained only after six hours, indicating a delayed absorption from the gastrointestinal tract.

In two patients, chloramphenicol, 44 mg./kg., was given every 8 hours for 3 days,

TABLE 1

CHLOROMYCETIN 22 MG./KG. BY MOUTH

Patient	Wt. (kg.)	Dose	Serum Levels μg./cc. at hr.							
			1	2	3	4	6	8	10	23
E.P.	24.9	550 mg.		7.4			4.2		1	
J.M.	24.9	550 mg.		2.6			6		1	
J.D.	23.1	500 mg.		7.8			6		2	
P.R.	11.5	250 mg.		6.4		7.6	6.2			
J.D.	21.5	500 mg.		10.6		9.2	4.2			
K.J.	28.6	600 mg.		7.2		6.8	6			
L.E.	25.9	550 mg.		9.8			6.4		3.4	
G.D.	15.9	350 mg.		14			6		1	
V.S.	16.3	350 mg.		13.6			5.4		1	
L.K.	12.0	250 mg.		9.6			2.5		2	
J.J.	12.2	250 mg.		3.8			2		2	
R.L.	7.9	200 mg.		7			5.6			

TABLE 2

CHLOROMYCETIN 44 MG./KG. BY MOUTH

Patient	Wt. (kg.)	Dose	Serum levels μg./cc. at hr.							
			1	2	3	4	6	8	10	23
G.D.	16.8	750 mg.	26	34	25	18.8	10.6	11.2		2.4
L.E.	25.4	1000 mg.	10.6	16.6	15.2	11.2	7.4	7.6		0
S.G.	31.8	1400 mg.		7			16		16.6	
M.G.	15.2	650 mg.		36			9.8		2.6	
V.S.	16.5	750 mg.		8.6			17.8		17.8	
J.J.	12.2	550 mg.		40			14.8		4.2	
J.R.	3.4	150 mg.		13.2			4		0	
R.G.	11.3	500 mg.		14.8			3.6			
J.D	21.5	950 mg.		28			10		2.4	

and serum levels were determined 2 hours and 8 hours after ingestion on each day of the experiment. The data are revealed in chart 2. On this dosage no significant cumulative effect is seen. The atypical results following the second dose on the second day in Patient 1 are unexplained.

Rectal Administration: Small gelatinous chloramphenicol suppositories were provided by the manufacturers. Great difficulty was encountered in effecting their retention. Serum levels produced in four patients who retained the suppositories were unsatisfactory. Dosage ranged from 22 to 44 mg./kg.

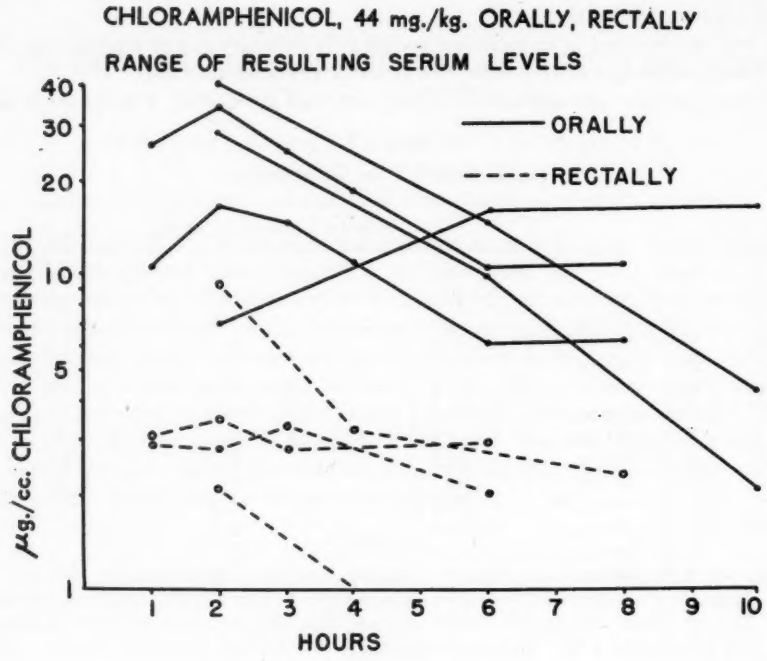

CHART 1

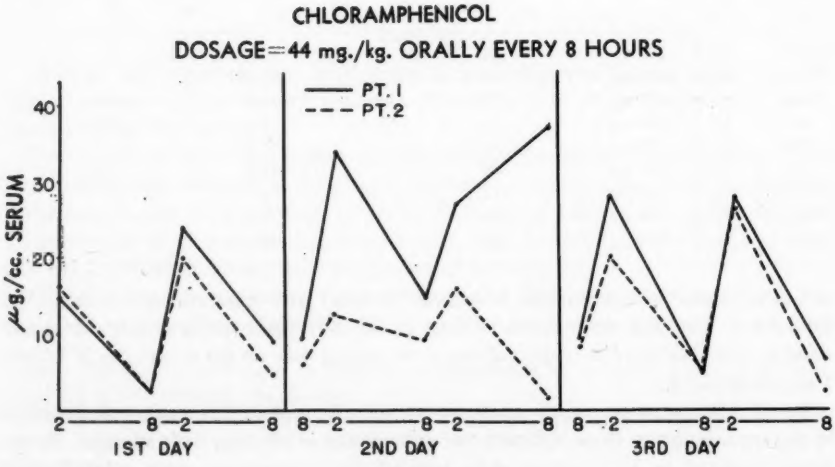

CHART 2

However, when perforated capsules were inserted rectally, little difficulty was encountered. Retention was satisfactory and there was no significant discomfort experienced by the patients. Serum levels were obtained in the four patients tested; the results are shown in table 3. These results are compared graphically with similar oral dosage in chart 1.

Diffusion into Cerebrospinal Fluid: Three children who were receiving chloramphenicol

TABLE 3

CHLOROMYCETIN CAPSULES/RECTUM

Patient	Wt. (kg.)	Dose	Serum levels μg./cc. at hr.							
			1	2	3	4	5	6	7	8
M.L.	4.2	250 mg.	3.1	3.4	2.8			2.9		
M.T.	4.3	250 mg.	2.9	2.8	3.3			2		
A.R.	10.3	500 mg.		9.4		3.2				2.3
J.J.	13.2	500 mg.		2.1		0				0

TABLE 4

CHLORAMPHENICOL, ORALLY 22 MG./KG. EVERY 8 HR. SIMULTANEOUS SERUM AND SPINAL FLUID LEVELS AFTER SEVERAL DAYS' THERAPY.

Patient	Serum μg./cc.	C.S.F. μg./cc.
1	3.0	2.0
2	7.0	3.6
3	21.8	8.9

orally in dosage of 22 mg./kg. every eight hours were subjected to simultaneous serum and spinal fluid level determinations after several days' treatment; levels were taken two hours after the last dose. None of these children had meningitis. The results, shown in table 4, reveal spinal fluid levels approximating 50% of the serum levels.

DISCUSSION

Previous investigation[4] in this laboratory has shown maximal serum concentrations of aureomycin to be produced by oral administration of this antibiotic in dosage of 11 mg./kg. body weight. Doubling the dose resulted in negligible increase in serum level. Furthermore, peak levels were obtained slowly, approximately four hours after ingestion, rarely were higher than 4 μg./cc., and were maintained for 6 to 8 hours. The implications are that aureomycin is absorbed slowly for a period of several hours after ingestion, and that there is a limiting factor in its absorption, so that increasing dosage beyond a certain point fails to promote an increase in serum level.

In the case of chloramphenicol, 11 mg./kg. is an inadequate dose to produce detectable serum levels. The peak serum levels produced by 22 mg./kg. range from 3.8 to 14 μg./cc. The implication is a wide variability in efficiency of absorption. Doubling the oral dose to 44 mg./kg. approximately doubles the peak serum level. This is in sharp contrast to the behavior of aureomycin, as is the fact that peak chloramphenicol serum levels are

usually reached two hours after ingestion, with steady drop in levels occurring shortly after the peak values have been attained. The assumption can therefore reasonably be made that absorption of chloramphenicol from the gastrointestinal tract tends to be prompt, and to have been completed within approximately two hours after ingestion.

Definite absorption from the rectum occurs when chloramphenicol capsules are inserted. Levels are approximately one-fifth of those obtained from comparable oral dosage. Rectal absorption appears to occur over a longer period of time than when the antibiotic is taken orally, since there is little change of serum level for as long as six hours.

Diffusion of chloramphenicol into cerebrospinal fluid is exceptionally good. The authors' data, showing spinal fluid levels of 50% of simultaneously obtained serum levels, compare with those found by Smadel et al.[5] This indicates a considerably greater capacity for penetration of the serum-spinal fluid barrier than is exhibited by aureomycin, with which antibiotic spinal fluid levels average one-fourth simultaneous serum levels.[4]

Antibiotic dosage is generally based on serum levels. From the data presented here, it appears that chloramphenicol, in order to produce detectable serum levels, must be given in oral doses in excess of 22 mg./kg. body weight every 6 to 8 hours. Forty-four mg./kg. given at these intervals is sufficient to maintain serum levels above 10 μg./cc., which concentration is above the in vitro minimal inhibitory concentrations of the majority of susceptible organisms, as shown by Bliss and Todd[6] and by Seligman and Wassermann.[7]

Correlation between in vitro and in vivo sensitivities in the case of chloramphenicol has not yet been demonstrated. Aureomycin, an antibiotic similar to chloramphenicol in many respects, has been studied from this standpoint by Klein et al.[8] These authors found the in vitro sensitivity of a strain of pneumococcus to be 5 to 10 times the serum level required to be effective in mice against heavy challenges of this organism. Whether such is the case in human infections has not been demonstrated. However, such information tends to suggest that serum levels of the magnitude attained in the present study may eventually be shown to be unnecessarily high. Until such data are at hand, however, it seems wise to give chloramphenicol in dosage sufficient to produce serum levels approximating the in vitro sensitivities.

Summary

Chloramphenicol is readily absorbed from the gastrointestinal tract. Peak serum levels, while usually reached within two hours, are occasionally not attained for six or more hours. In general absorption is markedly more rapid than in the case of aureomycin, which seems to be absorbed slowly over a period of several hours.

Eleven mg./kg. body weight, which is an adequate single dose of aureomycin, in the case of chloramphenicol produces serum levels too low to be detected by the authors' method. Twenty-two mg./kg. produces two hour levels averaging 8.3 μg./cc. and 44 mg./kg. raises this level to a mean of 22 μg./cc.

Rectal administration of perforated chloramphenicol capsules produces peak serum levels approximately one-fifth of those effected with comparable oral dosage.

Diffusion of chloramphenicol into cerebrospinal fluid occurs readily and after a few days administration spinal fluid levels, in three cases, were approximately 50% of the serum levels.

These data suggest that effective oral dosage of chloramphenicol ranges from 22 to 44 mg./kg./dose and that the antibiotic should be given at 6 to 8 hour intervals.

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Spanish Abstract

Estudios en la Absorción y Distribución de el Chloramphenicol

El chloramphenicol (cloromicetina) es rapidamente absorbido del tracto gastrointestinal. Concentraciones maximas de la droga en el suero se obtienen generalmente a las dos horas, aunque ocasionalmente pueden demorarse seís horas o más. En general là absorción es mas rápida que la de la aureomicina, la cual se absorbe mas lentamente por periodos de varias horas.

La administración de 11 mg./kg. de peso de chloramphenicol es insuficiente para producir concentraciones demostrables en el suero. Con dósis de 22 mg./kg. de peso se obtienen a las dos horas concentraciones promedios de 8.3 μg./cc., y con dósis de 44 mg./kg. de peso las concentraciones aumentan hasta un promedio de 22 μg./cc.

La administración rectal de capsulas perforadas de chloramphenicol produjeron concentraciones maximas en el suero aproximadamente la quinta parte de las obtenidas con dósis orales comparables.

La difusión del chloramphenicol en el liquido cefalo-raquideo ocurre rapidamente y a los pocos días de administración las concentraciones obtenidas en tres casos, fueron aproximadamente un 50% de las concentraciones del suero.

Estos resultados sugieren que la dosis oral efectiva del chloramphenicol oscila entre 22 y 44 mg./kg. de peso/dosis, administrada cada 6 a 8 horas de intervalo.

The Johns Hopkins Hospital

SYNDROME OF OVARIAN AGENESIS (CONGENITALLY APLASTIC OVARIES)

Short Stature, Multiple Congenital Abnormalities and High Urinary Gonadotropins in a Two Year, Eight Month Old Female

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NONE of the numerous cases reported in the literature of individuals with the syndrome of ovarian agenesis—short stature, various congenital abnormalities and high urinary gonadotropins—includes one that was diagnosed and completely studied prior to the age of puberty. The present investigator has had occasion to observe a young child with this syndrome in whom the tentative diagnosis was first made at the age of 2 years, 8 months, and confirmed at the age of 4 years, 7 months, when exploratory laparotomy and biopsy of an ovary disclosed aplasia of these organs associated with a rudimentary uterus. Thus it is demonstrated that the diagnosis of this syndrome can be made prior to the age of puberty before sexual maturation is expected to occur.

CASE REPORT

J. L. was first seen in the University of California Out-Patient Clinic at the age of 10 mo. because of a congenital deformity of the skin of the neck. She had been born at term following a normal delivery and had weighed 2.5 kg. At birth a large fold of extra skin on the neck posteriorly had been noted. This fold of skin formed a web which extended down to the shoulder and pushed the ears forward. The feet also were malformed at birth and were described as being "swollen." Although the deformity of the neck and of the feet had improved considerably since birth, some degree of abnormality was still evident at the time of the first examination in the Clinic. The child had been in excellent health, with a good appetite and a well balanced diet. Adequate amounts of supplemental vitamins had been given. Her first tooth had erupted at the age of 6 mo.; she had sat alone at 7 mo. and was able to stand at the age of 10 mo. The remainder of the past history was essentially negative.

Physical examination disclosed loose, redundant, extra folds of skin at the nape of the neck which spread in web fashion out toward the shoulders and above the hair line (Fig. 1). The anterior fontanel was still open. The ears had large protuberant pinna, but were otherwise normal. Four deciduous teeth had erupted. The genitalia were normal externally. Both feet had flattened arches, hammer-toe deformities of all toes, a mild degree of metatarsus varus with hallux valgus, and spatula-like nails which were raised from the nail bed and attached only at the base. There was normal mobility of the feet, but the entire foot was inverted in relation to the ankle joint and tibial axis.

When the girl was 2½ yr. of age, a plastic operation on the webbed neck was performed (Dr. Harry Blackfield). At this time the question arose of this being an instance of Turner's syndrome ("infantilism, congenital webbed neck, and cubitus valgus"), and she was referred to the present clinic by Dr. Robert F. Escamilla for further investigation.

When seen in the clinic at 2 yr., 8 mo. of age, she weighed 12.9 kg. and was 86 cm. tall.

The mother had noted that the child had always been shorter than the average child but the rate of growth had appeared to be normal. Both parents and a younger sibling were of normal height.

Physical examination revealed the plastic repair of the webbed neck (Fig 1B) and the persistence

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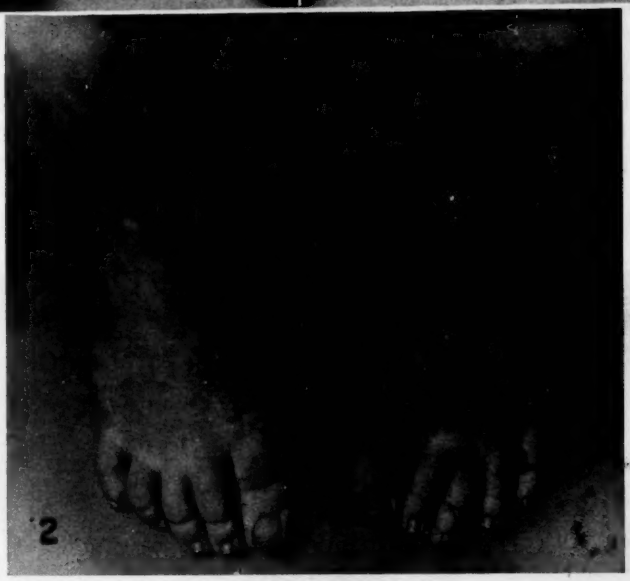

FIG. 1. A. J. L. before operation. Note webbed neck and feminine appearance. B. J. L. after operation.

FIG. 2. Appearance of feet with residual deformity of toes.

of the deformity of the feet (Fig. 2) but, according to the parents, this was much less marked than it had been when she was younger. She was able to walk and run without difficulty, and could wear regular shoes. At this time there was a questionable increase of the carrying angle of the arm (cubitus valgus). No abnormality of the heart was present. One month later a urinary gonadotropin assay was run and was found to be positive at 15 mouse units/24 hr.* Three out of 5 subsequent

* Performed by an ultrafiltration method.[1] By this method normal adult women have been found to excrete between 5 and 80 mouse u./24 hr., and no normal child has had as much as 5 u. under the age of 6 yr.

TABLE 1

EXCRETION OF URINARY GONADOTROPINS

Date	Age of Patient	Assay Level
February 1948	2 yr., 8 mo.	Positive at 15μ/24 hr.*
June 1948	3 yr.	Negative at 60μ/24 hr.
June 1948	3 yr.	Positive at 5μ/24 hr.
October 1948	3 yr., 4 mo.	Positive at 5μ/24 hr. Negative at 80μ/24 hr.
May 1949	4 yr.	Negative at 5μ/24 hr.
November 1949	4 yr., 6 mo.	Negative at 5μ/24 hr.
January 1950	4 yr., 8 mo.	Positive at 5μ/24 hr. Negative at 80μ/24 hr.
ADULT WOMEN		Positive at 5μ/24 hr. Negative at 80μ/24 hr.
YOUNG CHILDREN		Negative at 5μ/24 hr.

* μ/24 hr.—mouse u. in a 24 hr. specimen of urine.

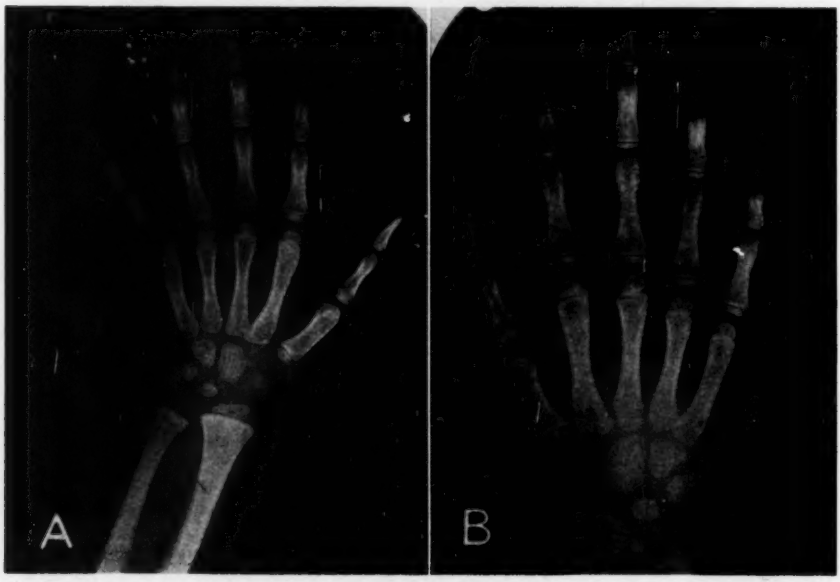

FIG. 3A. Chronologic age—3 yr., 5 mo.; bone age—3 yr., 3 mo. B. Chronologic age—4 yr., 8 mo.; bone age—4 yr.

assays of urinary gonadotropins also showed abnormally high levels (Table 1). At the age of 3 yr., 5 mo., the bone age of the wrist was 3 yr., 3 mo.[2] (Fig. 3A).

The patient was admitted to the hospital at the age of 4 yr., 7 mo., in order that rectal examination could be performed while she was anesthetized, and it was planned to perform a laparotomy if the internal structures were found to be abnormal. On admission her blood pressure was 108/76 mm. Hg; head circumference was 49.9 cm.; chest circumference 52.5 cm.; height 100 cm.; weight 15.5 kg. The physical examination otherwise was as noted on previous examinations (Fig. 4). The complete blood count was: Hgb., 13.2 gm./100 cc.; RBC count 5.09 million/cmm.; WBC count 12.0 thousand/cmm. with a normal differential count. The reactions to the tuberculin and Schick tests were negative. A routine urinalysis was within normal limits. Serum phosphorus was 5.4 mg./100 cc.; serum phosphatase 3 Bodansky u.; and fasting blood sugar 109 mg./100 cc. (normal by the method used). Roentgenograms

FIG. 4. J. L. Note good nutrition, stocky appearance and slight increase of carrying angle of arms.

of the skull demonstrated no disease. The pelvic inlet appeared to be gynecoid in type. RGs of the spine (Fig. 5) showed a scoliosis in the thoracic region with some anterior wedging of the lower vertebral bodies. The margins of the bodies were irregular and the intervertebral disc between the ninth and tenth vertebra was narrow. These changes were considered to be typical of those found in juvenile epiphysitis. In the lumbar area there were small bony projections arising from the superior surface of the lamina of the first and second lumbar vertebrae which appeared to be due to an error in development. A recheck of the bone age at the time this patient was 4 yr., 8 mo. old revealed that it was at the 4 yr. level (Fig. 3B)* of age. The 17 ketosteroid assay on a 24 hr. urine specimen was 1.12 mg. for 24 hr. An exploratory laparotomy was performed 5 days after admission by Drs. Daniel Morton and Donald Payne, who found a rudimentary uterus and elongated whitish ovarian streaks. Their report, in part, is as follows:

"A rectal examination under anesthesia failed to reveal any structures of the female genital tract in the pelvis. A small ridge of tissue not more than 0.5 cm. in diameter was felt in the midline and it was thought that this probably represented the uterus. The patient was prepared for laparotomy. A lower midline incision was made. General abdominal exploration was not carried out, except for

* At the age of 5 yr., 3 mo., the bone age was only 4 yr., 4 mo.

feeling the kidney region. Both kidneys were palpated and seemed to be approximately of normal size and in a normal position. Fallopian tubes on either side were found to be rather long, measuring approximately 10 to 12 cm. in length. The fimbriated ends of the tubes which were normal to gross inspection, were located high in the lumbar gutters and the tubes then descended toward the pelvis.

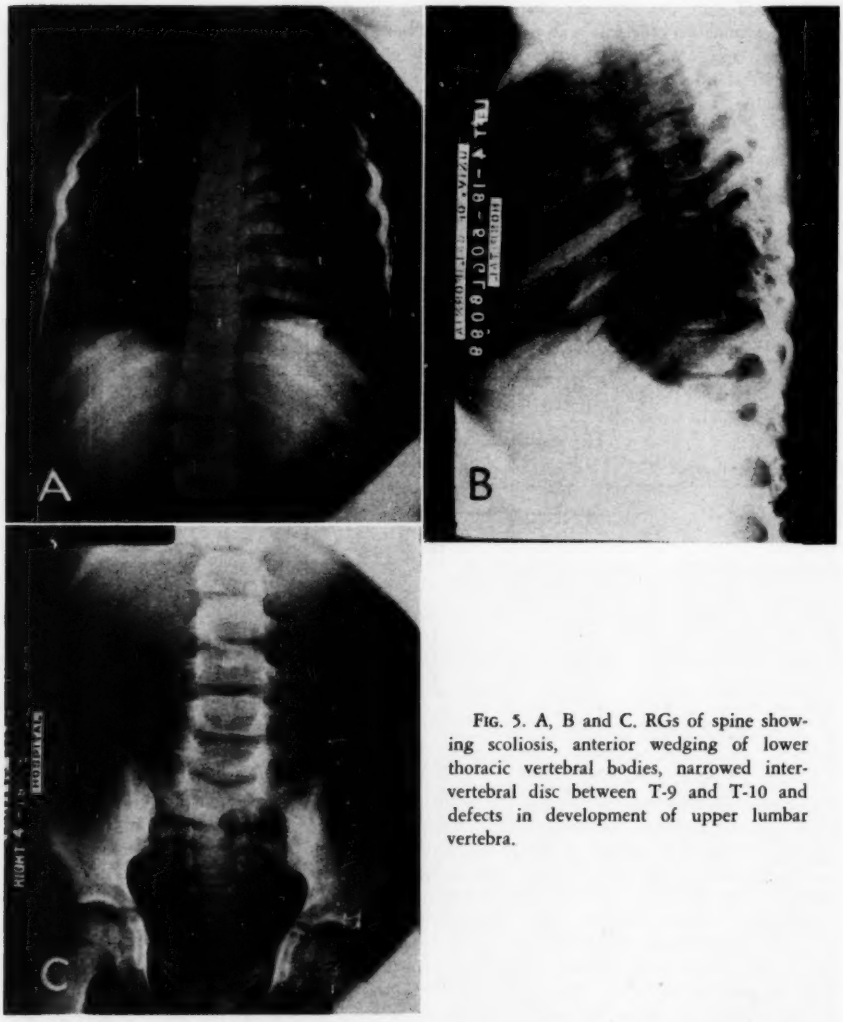

FIG. 5. A, B and C. RGs of spine showing scoliosis, anterior wedging of lower thoracic vertebral bodies, narrowed intervertebral disc between T-9 and T-10 and defects in development of upper lumbar vertebra.

They united in the midline, right behind the bladder, and in this region there was a bar of tissue approximately 0.5 cm. in diameter and 1.5 to 2 cm. in length. Attached to this bar of tissue were the round ligaments. The interpretation was that this bar of rather fibrous-feeling tissue represented the uterus. Immediately medial to the distal one-third of the Fallopian tubes on either side and lying rather high in the lumbar gutters were white streaks of tissue. The streak on the left measured approximately 3 cm. in length, and at its upper end was a small nodule of tissue approximately 0.5

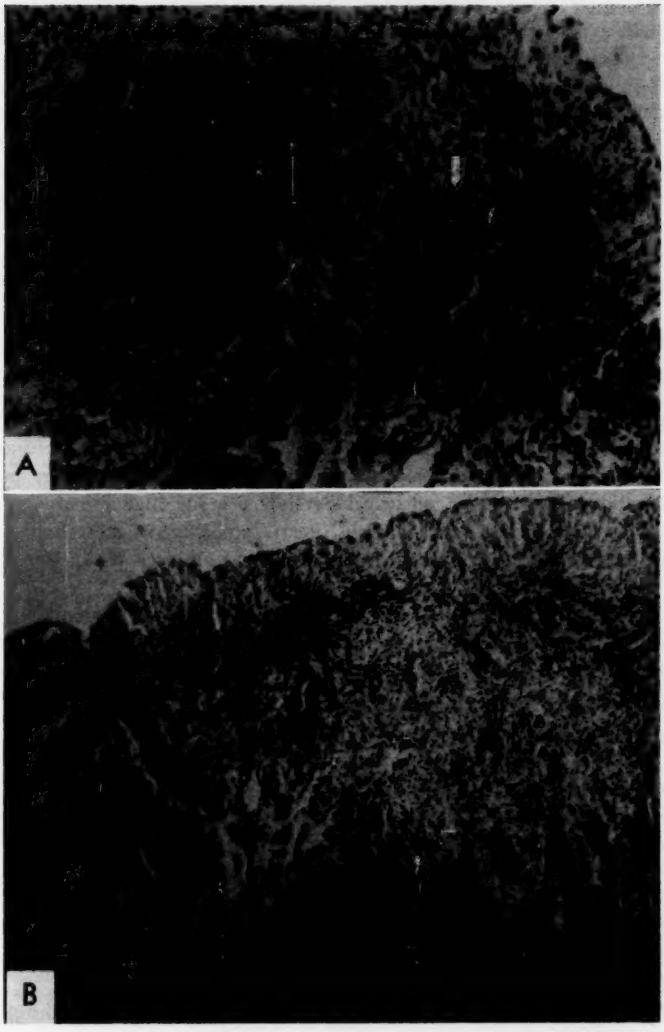

FIG. 6. A and B. Photomicrographs of ovary. There is no recognizable germinal epithelium or primordial ova.

cm. in diameter. The streak of whitish tissue adjacent to the right tube was also approximately 3 cm. in length and 0.3 cm. in width. No other structure could be found that had any of the characteristics of ovarian tissue. A small biopsy of the white tissue adjacent to the right tube was taken. No other abnormalities were noted in the pelvis. The appendix was lying in the right lumbar gutter, appeared rather long but was otherwise normal."

Microscopic examination of the biopsy material showed it to be characteristic of ovarian agenesis. It consisted of a dense fibrous stroma without any recognizable germinal epithelium. No primordial ova were seen. There were several small areas of fairly large polyhedral cells with clear refractile cytoplasm and varied-sized oval to round, somewhat vesicular, nuclei (Fig. 6).

The postoperative course was uneventful and the patient was discharged from the hospital 7 days after operation.

Discussion

The combination of shortness of stature and sexual infantilism, associated with hypoplasia of the ovaries, was first described by Kermauner[3] in 1912. Subsequently, isolated instances of this syndrome were reported, which were based on purely anatomic observations.[4–21] In 1938, Turner[22] reported the cases of seven girls from 15 to 23 years of age with shortness of stature who presented a syndrome of "infantilism, congenital webbed neck, and cubitus valgus." Although they were in an age group when sexual maturation might have been expected, their breasts, vaginae and uteri were infantile and menstruation had not occurred. Since assays of the urinary gonadotropins were not made, there is no proof that the condition was due to primary ovarian deficiency, but the similarity of Turner's cases with others subsequently reported in whom gonadotropins were increased makes it probable that their pathogenicity was identical, even though Turner ascribed the changes to a pituitary deficiency.

Varney and his collaborators[23] and Albright and his co-workers[24] established the important clinical and hormonal characteristics of this syndrome when they pointed out the combination of retardation of sexual development and high urinary gonadotropin titers. An increased urinary gonadotropin titer is probably the most important single finding in these cases, and has been observed in almost all cases in which it was investigated.

From a review of the literature, the most frequently described anatomic, biologic and clinical manifestations of the syndrome of ovarian agenesis in females after the age of puberty have been:

(a) Shortness of stature of moderate degree in most but not all cases;
(b) Good muscular development, the patients being strong and well nourished;
(c) Congenital anomalies, such as webbing of the neck, cubitus valgus, syndactylism, coarctation of the aorta and ocular changes;
(d) Rudimentary ovarian development;
(e) Increased urinary gonadotropins;
(f) Subnormal titers of urinary estrogens;
(g) Diminished 17-ketosteroids of the urine;
(h) Moderate retardation of skeletal maturation with delay in epiphyseal closure;
(i) Diffuse osteoporosis;
(j) Vertebral chondrodystrophia;
(k) Normal carbohydrate metabolism as indicated by the reaction to insulin-induced hypoglycemia;
(l) Primary amenorrhea;
(m) A decrease but not total absence of axillary and pubic hairs;
(n) Infantile breasts, uterus, vagina and labia.

Shortness of stature is a common but not constant finding in this syndrome. In many instances it has been difficult to ascertain from the published reports the period of life at which the growth retardation began but it appears likely that growth almost always was at a subnormal rate in most of the patients with this syndrome, and that the retardation only became obvious when the girls first went to school or had other contact with children of the same age when a direct comparison could be made. The average height of

these patients in adult life is approximately 140 cm. (55 inches) but some ultimately reach one of over 157.5 cm. (62 inches). Even the dwarfed individuals are stockily built and have good muscularity. Although the rate of growth in the patient reported here was subnormal between the age of 10 months and 2½ years, it was normal for the following two years (chart 1).

Lisser et al.[26] have pointed out that a characteristic "shield-shaped chest" was a frequent finding with the thorax being prominent anteriorally, broader than normal, with widely spaced nipples and with an increased antero-posterior diameter similar to the "bell chest" of emphysema. This "shield chest" tends to emphasize the clinical impression of stockiness.

Among the congenital abnormalities that have been noted in association with ovarian agenesis are cubitus valgus (increased carrying angle of the arm), congenital webbed

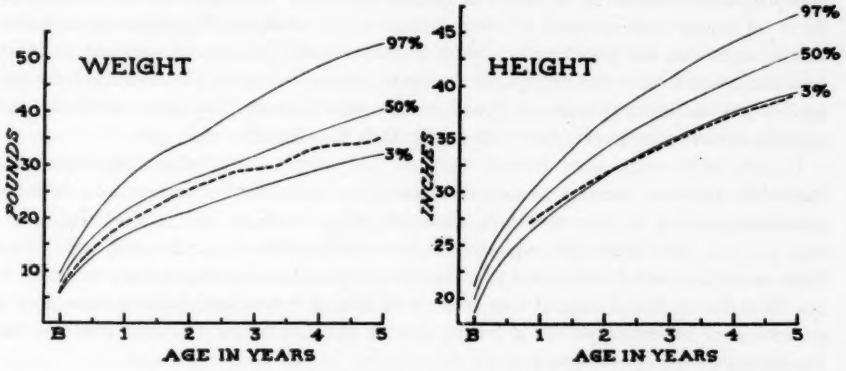

CHART 1. Patient J. L. Height and weight.[25]

neck, pes cavus at rest, congenital deafness, coarctation of the aorta, and ocular abnormalities including squint, ptosis, cataracts, tubular vision, mild exophthalmos and lack of retinal pigmentation. Of these, cubitus valgus and the congenital webbed neck were present in the patient reported here and, although they are not universally present, they are the two found most often in this syndrome.

Abnormalities in the skeletal structure are common and include osteogenesis imperfecta tarda, anomalous position of a toe, spina bifida occulta, abnormal development of ribs, fusion of the cervical vertebrae, osteoporosis and vertebral chondrodystrophia. During the first year of life the feet of the present patient showed flattened arches, hammer-toe deformities of all toes, a suggestion of metatarsus varus with hallux valgus and spatula-like nails, which were raised from the nail bed and attached only at the base. The entire foot was inverted in relation to the ankle joint and tibial axis.

Although no osteoporosis was noted in any of the bones, there were striking changes in the vertebrae (Fig. 5). These were considered to be typical of those found in juvenile epiphysitis, but are similar to those which del Castillo et al.,[27] on the basis of their anatomic characteristics, believed to be due to "chondrodystrophy." In the lumbar area there were small bony projections arising from the superior surface of the lamina which appeared to be due to an error in development. Del Castillo et al. also have pointed out that osteoporosis is a relatively common finding in the older females and when it does

occur it is diffuse and is predominant in the vertebrae and the ilium. This osteoporosis is similar to that observed in women after the menopause and it probably should be ascribed to estrogen deficiency. The osteoporosis may have been absent in the present author's patient because of the extreme youth of the child; it might appear at a later age.

An increase in urinary gonadotropins is the most important single clinical or laboratory finding in making the diagnosis of ovarian agenesis. Only the demonstration of the characteristic pathologic findings is more significant and in the present state of knowledge concerning congenital ovarian aplasia, the finding of a high urinary gonadotropin output would seem to be of paramount importance in establishing a clinical diagnosis, especially in those cases which are somewhat atypical.

The exact mechanism for the production of excessive amounts of urinary gonadotropins is not clear although Albright et al. suggested that it may result when the hypophysis, in the absence of the effect of ovarian hormones "becomes unbridled" and produces an exaggerated quantity of these substances. If Albright's hypothesis is correct it would mean that the preadolescent ovary produces small amounts of estrogens or other substances which keep the hypophysis in check, since even before her third birthday the patient was excreting amounts of gonadotropins which would have been normal for the sexually mature woman but were abnormally high for a child of her age.

Urinary assays were done several times on the patient and although they were performed by the same method on each occasion there was marked variation in the level of gonadotropins. On one occasion there were more than 15 mouse units in a 24 hour specimen of urine (an abnormally large amount for a child of this age) while two other times there were less than 5 mouse units.* The exact explanation for this marked variation is not clear but it would suggest that more than one determination should be made in a preadolescent patient suspected of having ovarian agenesis before it is concluded that the gonadotropins are not increased.

A delay in the bone age in relation to the chronologic age has been described in many patients, but the epiphyseal maturation was only questionably retarded in the present patient (Fig. 3).

Wilkins and Fleischmann[28] have reviewed the pathologic reports in the literature and point out that although the "streaked" ovaries are found in many of these patients, they are not the invariable finding since, in some cases, the ovaries were said to be "the size of orange seeds," and in others they were described as oval bodies. These authors further pointed out that anatomically in many cases it would appear that the gonads had developed but little, if at all, beyond the stage of the primitive genital ridge.

After reviewing the clinical, laboratory and pathologic findings in the reported cases, as well as this one, it may be concluded that just as webbed neck and other congenital anomalies are not indispensable for the diagnosis of ovarian agenesis, so, too, primary amenorrhea, lack of breast development, infantile appearance of external genitalia and diminution of pubic and axillary hair are not necessary parts of the picture since all these latter characteristics are normally absent in a prepubertal age. No single physical finding is present in every instance and even though primary amenorrhea and signs of sexual infantilism were noted in every case previously reported, it is obvious from this that the diagnosis can be made at a time of life when these findings are entirely normal.

The differentiation of the clinical picture of ovarian agenesis from that of other dis-

* See footnote on p. 369.

eases which disturb growth or modify the development of the sexual organs may be difficult. The most important condition to be considered is primary pituitary infantilism, which is also characterized by shortness of stature and retarded sexual development. The outstanding differential point is the urinary excretion of pituitary gonadotropins, which is absent in pituitary infantilism as contrasted with the decidedly high titers found in ovarian aplasia. Furthermore, the older patients suffering from ovarian aplasia are as a rule short of stature but not as tiny as pituitary dwarfs; they have more pubic and axillary hair than the latter; they usually are well nourished, with a stocky build and a broad, deep "shield chest" in contradistinction to the slender gracile Levi-Lorain type of skeleton typical of hypophyseal infantilism. The bone age is only slightly retarded in ovarian aplasia in contrast to the much greater retardation of pituitary dwarfism. Other congenital anomalies, such as coarctation of the aorta, webbed neck and cubitus valgus also aid in making the correct diagnosis, since they usually have not been observed in association with primary pituitary infantilism.

When it originates in childhood, eunuchoidism due to removal or ablation of the gonads is more easily diagnosed since females with this disorder tend to be tall and typically have disproportionately long extremities. The rate of the follicle-stimulating hormone excretion does not help to differentiate this condition from ovarian aplasia, since it is high in both.

Other causes of dwarfing, such as hypothyroidism, mongolism, severe malnutrition, childhood diabetes, renal rickets or congenital heart disease, may be readily ascertained by the clinical picture and the performance of the proper diagnostic tests.

There is no completely satisfactory interpretation of the association of shortness of stature with genital impairment and high urinary gonadotropins. Albright has offered the hypothesis that the impairment of growth is due to the fact that the production of adrenal androgens is less than that of normal adult females, but Wilkins and Fleischmann point out that if the stunting of growth were due to diminished adrenal activity in patients with ovarian agenesis, one would expect them to grow normally through the preadolescent period but to fail making an adolescent growth spurt. The case histories do not indicate that this is so. Wilkins and Fleischmann and Lisser et al. explain the occurrence in one syndrome of congenital anomalies involving such diverse structures as the gonads, skeleton, cardiovascular system and eyes on a genetic basis and are of the opinion that the deficient growth is due to a defect in the germ plasma rather than to an endocrine disturbance.

Summary and Conclusions

A proved case of the syndrome of ovarian agenesis, short stature, multiple congenital abnormalities and high urinary gonadotropins in a 2 year, 8 month old female is presented.

Congenital anomalies included webbed neck, abnormalities of the feet, a moderate degree of cubitus valgus and defects of the vertebrae.

Only slight retardation of epiphyseal development was present by the fourth year of life.

Because of the marked variations in the levels of urinary gonadotropins in this patient, it is suggested that more than one assay should be performed in a preadolescent girl before it is concluded that the gonadotropins are not increased.

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SPANISH ABSTRACT

El Síndrome de Agenesia Ovarica (Aplasia Ovarica Congenita); Reporte de un Caso

Se describe un caso auténtico de síndrome de agenesia ovarica ocurrido en una niña de dos años de edad, presentando estatura corta, anomalías congenitas múltiples y aumento de las gonadotropinas urinarias. Las anomalías congenitas observadas incluyeron "webbed neck," deformidades de los pies, grado moderado de cubitus valgus y defectos en las vertebras. Se observó un ligero retardo del desarrollo epifisario a los cuatro años de edad. Debido a las variaciones marcadas de las concentraciones de gonadotropinas urinarias observadas en este paciente, el autor sugiere que varias determinaciones deben hacerse en una niña pre-adolescente antes de concluir que las gonadotropinas no están aumentadas.

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CONGENITAL STIPPLED EPIPHYSES

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Galveston

CONRADI[1] in 1914, under the title "Chondrodystrophia Foetalis Hypoplastica," described a peculiar pattern of ossification of the epiphyses in an infant having achondroplasia. Fairbank[2] in 1927 again called attention to this unusual entity and 22 years later reviewed[3] the literature and found that 16 cases had been reported which appeared to fulfill the criteria of this syndrome. Raap[4] in 1943 reported four siblings whom he considered to have this symptom complex. Fairbank, however, did not include these patients in his review. Fairbank prefers the term "dysplasia epiphysialis punctata" while others use the expression "chondrodystrophia calcificans congenita" or "stippled epiphyses." The designation "stippled epiphyses" seems appropriate inasmuch as all patients do not have features of chondrodystrophy. Caffey[5] emphasized the need to differentiate patients exhibiting calciferous stippling of the growing cartilage without bodily disproportion from the patients with typical achondroplasia having similar abnormalities in the epiphyses. On the other hand, Fairbank in his study stated that dwarfism of the short limb type is a usual feature of the syndrome.

The characteristic feature of the condition is the presence of a number of discrete centers of calcification in many cartilaginous epiphyses and apophyses. The onset appears to be in fetal life and females predominate over males 2 to 1. Recognition of the disorder was made within the first 9 months of life in 14 of the 16 patients summarized by Fairbank, and in a few during the immediate postnatal period. Only 2 cases were discovered after the age of 2 years and one of these was alive at the age of 9 years. The majority of the patients died of pulmonary and/or urinary tract infections, and one of miliary tuberculosis. Although Fairbank could find no evidence of hereditary influence, Maitland[6] called attention to 2 female siblings with the disorder. Raap[4] also reported the condition in 3 siblings, and a fourth, 2½ years of age, had normal bony structure except for a few punctate densities in both wrists and ankles. Hünermann[7] in 1931 reported a case with this syndrome which he observed from the age of 3 weeks to 22 months. Roentgenograms at the latter age showed a marked reduction in the number of calcific densities although a few were still evident. The etiology remains obscure.

The presence of two infants with stippled epiphyses on the Pediatric Service of the University of Texas Medical Branch Hospitals afforded the opportunity of studying the clinical features of this rather rare syndrome.

REPORT OF CASES

Case 1: LRH (9910-F), a 5 wk. old white male infant, was admitted to the Children's Hospital of the University of Texas because of "short arms and legs and inability to straighten his knees," findings which were noted at birth. The prenatal period had been entirely free of any maternal illness and the birth was spontaneous at term without complications. Birth weight was 3.4 kg. In addition to the deformities of the extremities, the infant was noted to have bilateral cataracts. He was said to have had no symptoms of birth injury, respiratory difficulty, fever or convulsions. There

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had been no feeding problem, although he had failed to gain weight. He was breast-fed for 4 wk. and then placed on an evaporated milk formula. There was no family history of any similar skeletal deformity. He was the fifth child of normal parents. Two siblings had died in the immediate neonatal period of "congenital heart defects" and the other 2 are living and well.

Physical examination on admission disclosed an infant in only fair nutritional state but conspicuous because of shortened extremities and bilateral cataracts (Fig. 1). Weight was 3.4 kg.; length, 52 cm.; crown to rump length, 36 cm.; span, 42.5 cm.; head circumference, 36 cm. The anterior fontanel measured 4 x 6 cm., and the posterior fontanel 0.5 x 0.5 cm. The eyes revealed bilateral central lenticular opacities with radiating peripheral "spokes." The ears, nose, mouth and throat were not remarkable. The neck was short but mobility was unrestricted. The chest was of normal contour. Lungs and heart were without abnormality on auscultation and percussion. The abdomen was normal. The extremities showed bilaterally symmetric shortening of the arms, which measured 5 cm.

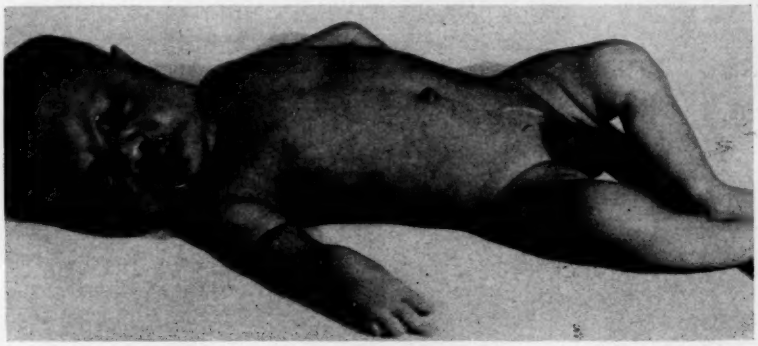

FIG. 1. Case 1. (LRH). Short proximal segments of extremities at age of 7 wk.

from the acromion to the olecranon. The forearms did not appear to be shortened. Passive movement of the shoulders appeared to cause pain but was unrestricted. No motor impairment of the upper extremities was demonstrable. There was also symmetric shortening of the thighs. Hip motion was unrestricted; however, on passive movement both knees lacked 45° of full extension.

Laboratory studies were within normal limits. Repeated urinalyses were negative. Sulkowitch tests for urinary calcium were negative. Hgb. 13.4 gm./100 cc., RBC 4.3 million/cmm. and WBC 9.0 thousand/cmm. The differential count showed 21% polymorphonuclear neutrophiles; 3% stab forms; 67% lymphocytes, 6% monocytes and 3% eosinophiles. Both Kolmer and Kahn blood serologic tests were negative. The serum alkaline phosphatase was 4.1 Bodansky units. Serum calcium and phosphorus were 9.0 and 7.1 mg./100 cc., respectively.

Extensive roentgen examinations were made of the skeleton which showed widespread epiphyseal calcific stippling, with severe deformities and shortening of the proximal long bones, findings typical of "congenital stippled epiphyses."

Central Skeleton: Fine calcific flecks, as indicated in Figs. 2 and 3, were found at the sites of epiphyses for the vertebral ends of the ribs, some of the transverse processes of the lower thoracic vertebrae, and most of the thoracic spinous processes. Most of the thoracic bodies, and those of L-1 to L-3, displayed a striking hypoplasia. Multiple tiny calcifications were in the sacral alae also.

Upper Extremities: There was enlargement of the proximal and distal humeral epiphyses in which masses of tiny irregular calcifications were seen, as shown in Fig. 4. Amorphous sheets of calcium density were also found in the proximal humeral epiphyses. The humeri were drastically shortened and their metaphyses were splayed. There were a few scattered calcific flecks at the head of each radius and in the wrists. The structure of the shafts of the bones of the forearms and hands was normal, as indicated in Figs. 4 and 5.

Lower Extremities: The acetabular sockets contained masses of small calcific densities which appeared to extend along the ischia to the tuberosities, as seen in Fig. 6; these masses apparently accounted for the dislocation of the hips. The capital and trochanteric epiphyses of the femora, the

patellar cartilages, the proximal and distal tibial epiphyses and the epiphyses of the tibial tuberosities displayed similar collections of small, irregular, discrete calcifications. The femora were only slightly shortened, but their metaphyses were wide and the upper ones displayed medial "beveling." The proximal tibial metaphyses were similarly widened. Although the knee joints appeared widened they were not thought to be dislocated. The feet appeared normal except for 2 small dense calcifications, one linear and one round, both of which appeared to be in the subcutaneous tissue of each heel, and apparently not in tendon or muscle.

Interpretation: This is a classical example of the entity, which is characterized by punctate calcifi-

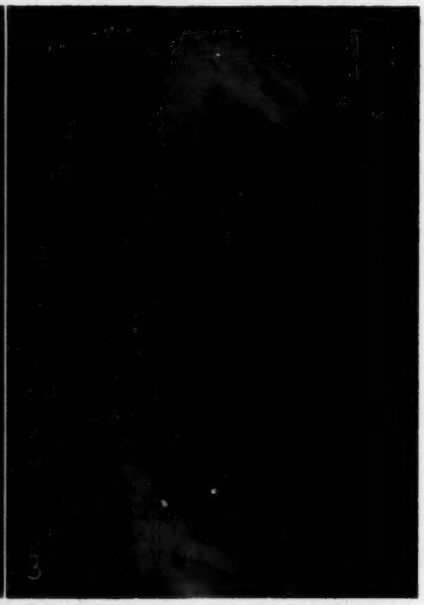

FIG. 2. Case 1. Antero-posterior RG of torso with calcific stippling of secondary centers along cervical and thoracic spine, shoulders and hips, sacral alae and ischia. FIG. 3. Case 1. Lateral RG with small thoraco-lumbar vertebral bodies.

cations in many epiphyses and changes in the shafts of the proximal long bones. Primary centers of ossification appear to be affected as evidenced by stippling in the wrists and by hypoplasia of the bodies of the thoracic and upper lumbar vertebrae. Although the initial diagnosis was dwarfism of the achondroplastic type, further study of the RGs seemed to establish the diagnosis of stippled epiphyses. It appears to be an entity distinct from chondrodystrophia fetalis (achondroplasia) in that shortening of the extremities is evident only in the proximal segments. On the other hand hypoplasia of the vertebral bodies with the findings in the extremities may suggest congenital stippled epiphyses to be a variant of chondrodystrophia foetalis.

The subsequent hospital course was remarkable only for the fact that the infant failed to gain weight despite what appeared to be an adequate intake of food and the absence of any gastrointestinal lesion. He was discharged after 24 days and failed to return for follow-up examinations in the outpatient clinic. A communication from the family revealed that the infant died of "pneumonia" 4 mo. after discharge. No postmortem examination had been performed.

Case 2: JLC (7255-G), a premature white male infant, was admitted to this hospital at 3 days of age with the chief complaint of "prematurity and feeding problem." He was the product of a 7 mo. complicated pregnancy, the mother having suffered from frequent and severe nausea and vomiting, as well as several "colds with fever" during the first trimester of pregnancy. During the last 3 of

the 7 mo.' gestation there was a mild but persistent bloody vaginal discharge which was termed a threatened abortion. She had edema of the face and legs during the last month of pregnancy and 2 wk. prior to delivery, she had a rash on the extensor surface of the right hand which resembled "poison oak" eruption. Her last menstrual period was 7 mo. prior to delivery.

The mother began having ineffectual uterine contractions the morning of delivery, and when the fetal heart rate was noted to decrease to 96/min. and remain slow, it was decided to deliver

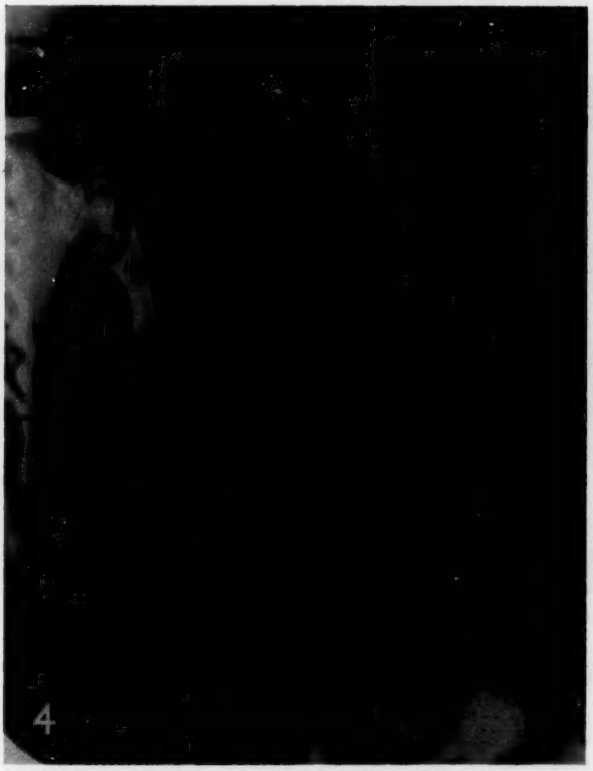

FIG. 4. Case 1. Both upper extremities with masses of discrete calcifications of epiphyses; there is extreme flaring at metaphyses and marked shortening of each humerus.

the infant by cesarean section. At the time of delivery the physician noted an excessive amount of amniotic fluid (polyhydramnios). The infant was estimated to weigh 1.5 kg., was inactive and cyanotic. Respirations were slow and the respiratory tract appeared to be obstructed. The infant's upper airway was aspirated and he was placed in an oxygen tent. His color improved but he remained listless and weak. He nursed poorly and was maintained by gavage feedings, but was said to have vomited several times during the 1st 24 hr. of life. The vomitus was described as frothy bloody material. He was maintained in an incubator with oxygen and parenteral fluid supplements at a local hospital until his admission to the premature nursery of the Children's Hospital.

The family history revealed the father to be 28 and the mother 22 yr. of age, both living and well. The patient had a healthy brother 2½ years of age. Another sibling had died en route to the hospital at the age of 9 mo. of "acute leukemia."

On admission the premature infant was small and inactive. He had a weak cry, a shallow respiration and a protuberant abdomen. Weight, 1.7 kg.; length, 41 cm.; head circumference, 32 cm.; chest

circumference, 26 cm. Temperature was 38° C. The anterior fontanel measured 1 x 2 cm., with over-riding of the edges of the posterior fontanel. The facies was unusual with a flattened nose and a conspicuous absence of the bridge of the nose, suggestive of lues. There was occasional sucking of the tongue, which protruded slightly. The nares were small and partially obstructed. The palate was high and arched. The eyes were not remarkable and there was no evidence of cataracts. The chest, lungs and heart were normal. The abdomen was protuberant and tympanitic to percussion. The liver and spleen were not enlarged. The testes were not palpable in the scrotum. The extremities were in proper proportion to the rest of the body, although the fingers were short and stubby. The second and third toes were elevated, and the fourth and fifth toes were curved medially under them

FIG. 5. Case 1. Punctate carpal calcifications; metacarpal and phalanges are of normal length.

bilaterally (Fig. 7). There was no limitation of motion, nor evidence of pain on passive movement of the joints of the extremities.

Laboratory studies revealed repeatedly negative urinalyses. Hgb. 17.7 gm./100 cc., RBC 5.2 million/cmm. and WBC 8.1 thousand/cmm., with a differential count of 20% polymorphonuclear neutrophiles, 68% lymphocytes, 8% monocytes and 4% eosinophiles. Cerebrospinal fluid examination was normal and blood Kolmer and Kahn serologic tests were negative. The serum calcium and phosphorus were 9.5 and 6.1 mg./100 cc., respectively, and the alkaline phosphatase was 4.9 Bodansky units. The total serum protein was 4.4 gm./100 cc., with albumin of 3.7 and globulin of 0.7 gm./100 cc., respectively.

Roentgenographic surveys of the skeleton, made on the 42nd hospital day and at postmortem 19 days later, disclosed a widespread calcific stippling, symmetrically distributed, at sites of primary and secondary ossification centers, and of the thyroid cartilage. The detailed roentgenographic findings are presented below:

Neck: A group of tiny dense calcifications was found in the region of the thyroid and cricoid cartilages, as shown in Fig. 8.

Central Skeleton: The skull and facial bones appeared normal, as indicated in Figs. 8 and 9. The vertebral bodies of C-2 to C-7, inclusive, were absent in part or wholly, and partially replaced by calcific discrete stippling. There was a kyphosis at C-7 to T-1 (Fig. 10). Each lumbar body bore a single tiny calcific density. The body of S-2 was deformed and those of S-4 and S-6 and the entire coccyx were replaced completely by discrete calcific flecks. Similar densities appeared to replace the articular processes of S-1 and were also in the sacral alae (Fig. 11).

Ribs: A single tiny calcified density was at the posterior end of the right 9th, 10th and 11th ribs and the left 10th rib (Fig. 11).

Sternum: The second sternal segment was replaced by a small round discrete calcification as seen in Fig. 10.

Upper Extremities: Multiple tiny calcific foci appeared at the sites of the coracoid processes of the scapulae, the distal epiphyses of the humeri, the midcarpus areas and the proximal ends of the metacarpals. Among the fingers, only the epiphyseal end of the distal phalanx, right middle finger,

FIG. 6. Case 1. Epiphyseal stippled calcifications in pelvis, hips, knees and ankles. Those in hips occur in large cartilaginous masses which produce appearance suggestive of dislocation of joints. At knees they are anterior, in chondral masses at sites of patellae, and in aggregates larger than normal patellar cartilages. Flaring of femoral and proximal tibial metaphyses is present and there is some "beveling" of proximal ends of femora. Modeling of bones of legs is normal except for excessive flaring of proximal ends of tibiae.

showed a similar change. The metacarpals and several phalanges were grossly deformed, with crenellation of their proximal margins and relatively square contours (Fig. 12).

Lower Extremities: The pelvic bones were normal in contour and structure. Small discrete calcifications were found at the site of the greater trochanter, bilaterally, as indicated in Fig. 13. The proximal tibial secondary centers were not yet visible. A small group of tiny calcifications was seen in the medial aspect of the left tibial distal epiphysis. Similar groups were in the tarsal regions,

widely distributed, as noted in Fig. 14. Metatarsals and phalanges showed structural deformities similar to those of the corresponding bones of the hands.

Interpretation: It is noteworthy that the proximal long bones of all extremities displayed no evidence of shortening or metaphyseal deformity, unlike the appearance usually found in this disorder. Nevertheless, the punctate, tiny calcifications widely distributed in the epiphyses, but not in areas of membranous bone, lead to the classification of this case as stippled epiphyses. Here, as in other

FIG. 7. Case 2 (JLC) at 7½ wk. of age.

reported cases, some of the stippling occurred in epiphyses which normally would not be expected to appear until later in life. None of it resembled the normal ossification process. The presence of normally formed proximal long bones in the upper and lower extremities appeared to indicate no interference with their development, at least until late in fetal life. On the basis of these findings the diagnosis of stippled epiphyses was established.

The course in the hospital was characterized by marked feeding difficulty with repeated episodes of vomiting and regurgitation several times daily. He was given an evaporated milk formula of 20 cal./oz. during most of his hospital stay. His weight gain was slow but consistent; the maximum weight was 2,520 gm. On the 65th day of life, he died suddenly; the immediate cause of death was thought to be aspiration of secretions and vomitus. At autopsy a small amount of vomitus was found in

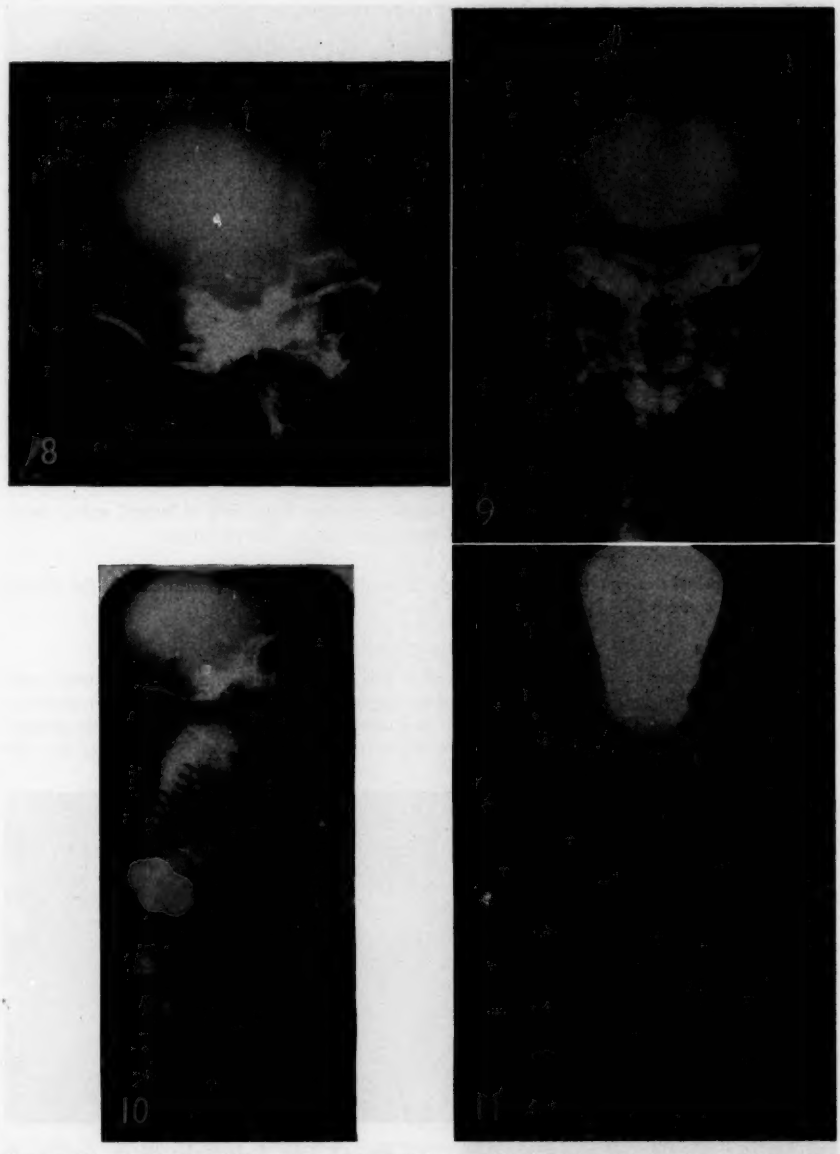

FIG. 8. Case 2. Discrete calcifications are formed in thyroid cartilage and in some secondary centers of cervical spine.

FIG. 9. Case 2. No abnormality of membranous bones of skull, nor of facial bones.

FIG. 10. Case 2. Bones of extremities are well modeled; there is calcific stippling of sacro-coccygeal bodies, and small midsternal calcification is present.

FIG. 11. Case 2. Antero-posterior RG (post mortem) with normal proportions of body and limbs.

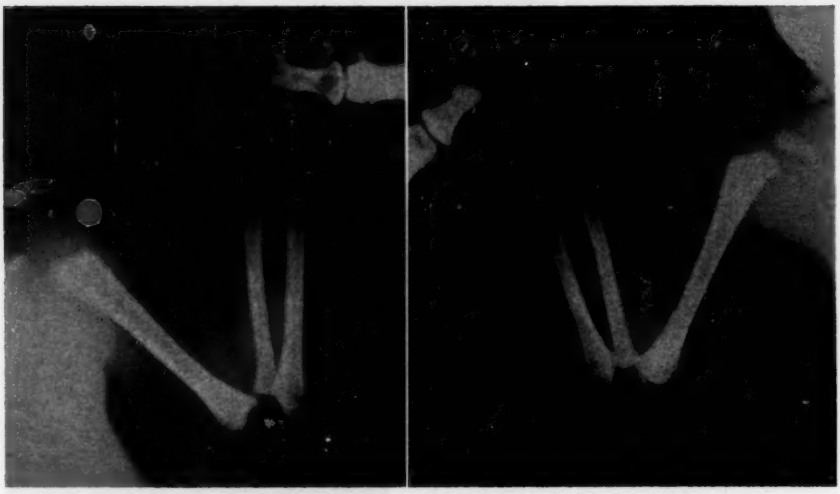

FIG. 12. Case 2. Fine stippled calcifications at coracoid processes, distal ends of humeri and in carpi, with crenelated deformities of metacarpals and several phalanges.

the tracheobronchial tree, but this was not thought to be sufficient to cause his death, hence the definite cause of death could not be ascertained.

AUTOPSY FINDINGS

Gross Examination (2 hr., 15 min. after death): The body was that of a 65 day old white male infant. Weight 2,520 gm., length 47 cm.; head to symphysis pubis measured 29 cm.; symphysis to heel measured 17 cm. The body was symmetric and unembalmed and rigor mortis was not present. Head circumference was 35.5 cm.; pupils were dilated to an equal 4 mm. each; the nose was flat

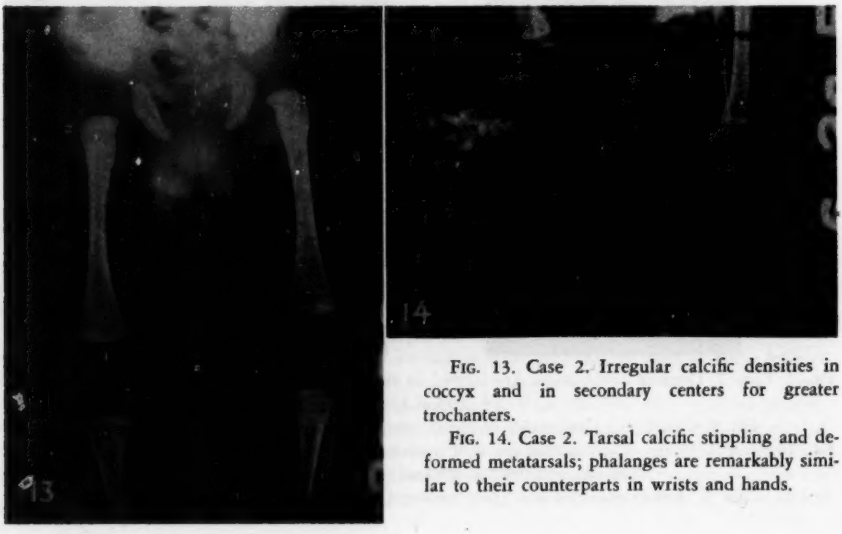

FIG. 13. Case 2. Irregular calcific densities in coccyx and in secondary centers for greater trochanters.

FIG. 14. Case 2. Tarsal calcific stippling and deformed metatarsals; phalanges are remarkably similar to their counterparts in wrists and hands.

and no teeth were present. The upper arms measured 7.5 cm., while the forearms measured 7 cm.; span, from finger tip to finger tip, measured 44 cm. The thighs and legs measured 9 cm. each bilaterally. There was a deformity of the second and third toes, in which the third toe was curved under the second toe bilaterally. No other abnormalities were noted on external examination. Upon opening the abdominal cavity the organs were in normal position and there was no fluid or exudate present. Within the thoracic cavity were found a normal thymus, and viscera in normal position. There was no fluid or exudate within the pleural spaces and the surfaces of the pleura were smooth

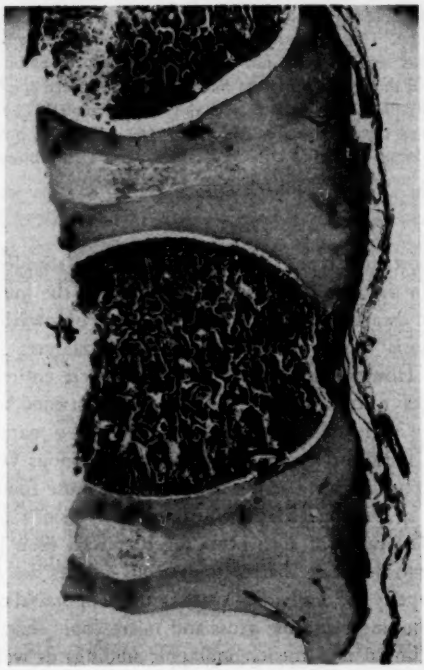

FIG. 15. Case 2. Photomicrograph of longitudinal section of lumbar vertebrae (stained with hematoxylin and pyloxine) with irregular pattern of bone formation and foci of degeneration in fibrocartilage. (× 12)

and glistening. The pericardial sac contained a small amount of clear, straw-colored fluid. The heart was of normal size and the myocardium was of normal consistency; the coronary ostea were patent. The walls of the ventricles measured 5 mm. on the left and 3 mm. on the right. There was no epicardial or valvular abnormality. The lungs revealed a slightly hemorrhagic external surface but the visceral pleura was smooth and glistening. On cut surface was noted a slight amount of aspirated formula within the bronchi. There was a generalized atelectasis present which was probably the result of incomplete expansion from birth. The liver was of a normal purple-brown color and the edges were slightly rounded and of soft consistency. Spleen was of normal color and consistency. Gastrointestinal system was negative except for conspicuous mesenteric lymphadenopathy. Pancreas, adrenal glands and genitourinary system showed no abnormality. The head was not opened and thus the central nervous system was not examined. Osseous system: the examination of the vertebrae revealed them to be grossly deformed. The usual rectangular, sharply demarcated bodies of the vertebrae were lacking. The bodies were ovoid in structure with ragged, ill-defined edges and in many

instances had multiple foci of calcification and ossification. These abnormalities were particularly prominent in the lumbar and sacral regions. The pelvis did not appear abnormal. There was no abnormality of the costochondral junction.

Microscopic Examination: The histologic picture of longitudinal sections of the vertebrae showed an irregular pattern of bone formation and within the fibrocartilage there were foci of degeneration which, in the hematoxylin and pyloxine preparation, suggested mucoid degeneration, as indicated in Fig. 15. These features were most prominent in the dorsal and lumber vertebral bodies. Sections of the ilium and of the costochondral junctions failed to reveal any specific changes. The lungs showed moderate congestion. Many alveolar spaces were filled with blood. There was no evidence of a pneumonia nor aspiration. The alveolar septa were thickened. Liver, spleen, kidneys, heart, pancreas, adrenals and thymus sections were not unusual. Summary of pathologic interpretation: (1) irregular bone formation of the vertebral bodies, consistent with stippled epiphyses (chondrodystrophia calcificans congenita): (2) phalangeal deformity of the toes, congenital; (3) mucoid type of degeneration of the fibrocartilage of the intervertebral substance; (4) premature, born after 7 mo.' gestation; (5) hemorrhage into the lungs-focal; (6) clinical diagnosis with roentgenographic findings compatible with stippled epiphyses (chondrodystrophia calcificans congenita).

Discussion

Dwarfism, of the short limb type, is the usual finding in stippled epiphyses. This feature was outstanding in the first case reported here, so that the initial clinical impression was chondrodystrophic dwarfism. There was no evidence of dwarfism in Case 2 and for this reason the diagnosis was uncertain. The lack of cataracts also tended to weigh against this diagnosis. However, the histologic features were entirely consistent with the diagnosis. Harris[8] cites a case of Thursfield and Lightwood,[9] that was designated "stippled epiphyses," with histologic findings consisting of a marked irregularity of the vertebral bodies, with mucoid degeneration of the cartilaginous vertebrae. In Case 2 of the present study, the changes were somewhat similar to those found in the case cited by Harris, but were not as pronounced. The primary perversions of growth in infancy assume many forms. The rarity of such cases, together with their pleomorphism of patterns makes it difficult to delineate sharply the various entities described in the literature. In order to classify properly any individual case, a careful appraisal of the clinical features, the roentgenographic findings, and the gross and microscopic characteristics is necessary. On the basis of the clinical and roentgenographic findings as well as the similarity of the histologic features it seems reasonable to classify Case 2 reported here in the same category as the case cited by Harris. Flexion contractures of the hip, knee or elbow were present in several earlier cases and Case 1 of this study did have this finding in the knee joints, with the inability fully to extend the knees, whereas Case 2 showed no evidence of contractures nor limitation of motion of any of the joints on passive movement. Thickening of the skin was noted by Bateman,[10] but this finding was not present in either of the two infants reported here. The head has shown no consistent or characteristic features, having been described as normal, macrocephalic, microcephalic and/or bossed. The fontanel is usually described as large, which feature was present in both infants in the present study. Bilateral congenital cataracts have been especially prominent in the British cases, being present in 6 of 10 cases; only one case with cataracts is mentioned by writers of other countries. Case 1 of this study had this finding whereas Case 2 did not exhibit any evidence of cataracts. The intellect has been described as dulled, even to the extreme of mental deficiency. Neither of the authors' subjects gave the impression of mental retardation; however, neither was seen beyond the age of 2 months. General weakness and failure to thrive have been outstanding observations, and both cases bear

out this impression. Serum calcium and phosphorus values in earlier cases were stated to have been normal, and these two infants had normal values. Of interest is the predominant incidence of the condition in females in contrast to males in previously reported cases, while both the authors' patients were males. It is noteworthy that patients with this syndrome display prematurity of calcium deposition in addition to the irregularity of the calcific stippling.

Harris[8] states that the bones of the hands less frequently show stippling than the elbow and pelvic girdle, but no other remarks were made of the hands. In Case 2 of the present study, crenelation of the margins of the metacarpal and several phalanges of the hands was a prominent finding. The presence of these small bone deformities in Case 2 has not been described in cases previously reported. This finding is apparently a further variant in this group of dystrophies, all of which may be manifestations of prenatal endocrine and/or metabolic influences, as suggested by the work of Duraiswami.[11]

The diagnosis of stippled epiphyses must depend on roentgenographic examination. The differentiation of this entity with the discrete stippling, as opposed to the mottling and epiphyseal irregularity seen in dysplasia epiphysialis multiplex, is quite distinctive. The irregularities of ossification occasionally seen in hypothyroidism has been designated as "stippled epiphyses" by Wilkins,[12] but in this condition the stippling appears later in life. Shortened proximal segments of the extremities and bilateral congenital cataracts, when present, give substantial support to the diagnosis of congenital stippled epiphyses.

Summary

Two infants, one full term and the other premature, presented symptoms of "congenital stippled epiphyses" (dysplasia epiphysialis punctata, chondrodystrophia calcificans congenita). The outstanding characteristics of the entity are the presence of multiple, discrete, dense calcifications in many cartilaginous epiphyses and apophyses. The diagnosis, necessarily, rests upon roentgenographic examinations.

Acknowledgment

The authors wish to acknowledge the assistance of Dr. Frank M. Townsend and Dr. V. A. Stembridge of the Department of Pathology, University of Texas, in interpretation of the pathologic findings.

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SPANISH ABSTRACT

"Congenital Stippled Epiphyses"

Se describen dos niños, uno a término y el otro prematuro presentando síntomas de "congenital stippled epiphyses" (Chondrodystrophia calcificans congenita, dysplasia epiphysialis punctata). Los síntomas caracteristicos de ésta entidad clinica consisten en la presencia de calcificaciones múltiples, discretas y densas en las epifisís y apefisís cartilaginosas. Necesariamente, el diagnóstico de estos casos depende del exámen radiografico. El niño a término presentó un acortamiente de los huesos largos proximales de las extremidades y catarata bilateral congénita. Se realizó un estudio necropsico en el niño prematuro. Las caracteristícas histologícas fueren similares a las previamente descritas, es decir, irregularidades en la formación del hueso, con areas sugestivas de degeneración mucoide la cual fué mas prominente en los cuerpos vertebrales.

University of Texas—Medical Branch

OUTBREAK OF ACUTE NEPHRITIS IN ADOLESCENT SCHOOLBOYS

By C. HENRY KEMPE, M.D.,* RICHARD W. OLMSTED, M.D., AND EDWARD C. CURNEN, M.D.
New Haven, Conn.

THE occurrence of acute nephritis in groups of associated persons has been noted in a variety of different circumstances. Among soldiers it has been recognized frequently and referred to as trench or war nephritis.[1-5] It has also been encountered among adult inhabitants of congested tenement buildings[6] and among families in which several children developed the disease simultaneously or in rapid succession.[7-11] To account for multiple cases of nephritis within a family, a "familial predisposition" to nephritis has been emphasized; in other groups, cold and damp surroundings and poor nutrition have been suggested as contributory factors. The development of nephritis following scarlet fever or other streptococcal infections has been observed frequently, and many students of the disease have expressed the opinion that nephritis is, in some obscure manner, caused by streptococcal infection.

It is the purpose of this paper to report an outbreak of acute nephritis which occurred among adolescent boys who were students at a private day school and to present the results of investigations carried out in relation to this episode.

MATERIALS AND METHODS

Clinical and Epidemiologic Study: The subjects of the investigations were white American schoolboys, 11 to 14 yr. of age. Information was sought first by visiting the school which they attended. The school authorities were interrogated, attendance records were reviewed, and the boys themselves were questioned and examined. Further information was obtained by interviewing parents and the family physicians of boys who had been ill and by scrutinizing the clinical records of each boy who was admitted to a hospital during the period of study.

In addition to the collection of pertinent clinical and epidemiologic data, specimens of urine and blood and cultures of the nasopharynx were obtained from as many students as possible among those who were included in the investigations.

Urinalyses: A specimen of urine was collected from each boy who was in attendance at the time of the first survey at the school on March 31, and additional specimens were obtained from certain boys on several subsequent occasions. For microscopic examination, specimens of urine were spun for 2 min. at 1000 rpm in a horizontal centrifuge. The sediment of each specimen was then examined under the high dry lens (magnified approximately 400×) and any cells found to be present were enumerated. Hematuria was classified from + to ++++ as follows:

\+ = 1-5 RBC/high dry field
++ = 6-10 RBC/high dry field
+++ = 11-15 RBC/high dry field
++++ = > 15 RBC/high dry field

In certain instances the RBC in urine collected during a 12 hr. period overnight were counted according to the method of Addis. A calculated total of one million or more RBC in the volume of urine excreted during the 12 hr. period was considered to be definitely abnormal.[12]

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The presence of albumin was determined by boiling a sample of the urine (filtered if cloudy) for 1 min. and inspecting its appearance against a dark background. Acetic acid (5%) was added to dissolve phosphates. Positive reactions were recorded on a scale of ± to ++++ as follows:

± = Trace of cloudiness
+ = Definite cloudiness without flocculation
++ = Cloudiness with flocculation
+++ = Dense cloudiness with heavy flocculation
++++ = Marked precipitation or solidification

Albuminuria of + or less was not considered to be abnormal in the absence of hematuria; ++ or more was regarded as definitely abnormal.

Bacterial Cultures: Material for culture was obtained from the nose by introducing the cotton tip of a flexible wire swab through the nares to the posterior nasopharynx and from the throat by using an ordinary swab applied to the oropharynx. Cultures were made on blood agar plates and in beef heart broth containing 2% rabbit blood. Preliminary identification of Str. beta hemolyticus was based on the appearance of the hemolytic colonies and the microscopic characteristics of the organisms.* Gram cocci, tentatively identified as hemolytic streptococci, were isolated in pure culture, and an attempt was then usually made with each strain to determine the serologic group and type according to the methods of Lancefield.*

Serologic Tests:* Specimens of blood collected from individual students were allowed to clot and were then centrifuged. The serum was separated and stored at -10°C. Serum was heated at 56°C. for 30 min. before tests. The antistreptolysin "O" content was determined by the method originally described by Todd,[13] as modified by Hodge and Swift.[14] Antistreptokinase in serum was estimated as described by Kaplan.[15] Antihyaluronidase determinations were made using a mucin clot prevention technic described by Quinn,[16] which represented a modification of methods reported by McClean[17] and Friou and Wenner.[18]

Clinical and Epidemiologic Features

A 14 year old boy, I.F., was admitted to the Grace-New Haven Community Hospital with acute glomerular nephritis. Eleven days later his best friend, S.F., was admitted to the same hospital with a similar illness. He, in turn, called attention to a third boy, R.O., who three weeks before had been admitted with severe nephritis to a different hospital in the city. This patient led to the discovery that a fourth boy, H.K., was under treatment at home for nephritis of moderate severity which had developed following an episode of acute pharyngitis. A summary of the clinical findings in each patient's case is appended.

The development of nephritis at approximately the same time by these four adolescent boys who were all classmates in school seemed unusual. Inquiries concerning the circumstances under which these boys became ill revealed no obvious contributory factors in their home environment and no record of illnesses in other members of their respective families to suggest a "familial predisposition" to nephritis. An investigation was, therefore, undertaken to determine the incidence and, if possible, the cause of nephritis among the students in the school which they attended.

The school is an old institution exclusively for male students. It has modern buildings and facilities, and is well situated on high ground near the outskirts of New Haven in a location where "dampness" is minimal for the geographic area. The students are in attendance only during daytime. They live at home in the city or its vicinity, generally in favorable economic and social conditions. They represent a variety of different national backgrounds, without a predominance of any one in particular.

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The students are distributed into a junior and a senior school comprising the lower and upper three classes or "forms," respectively. At the time of the present study the total enrollment was 220. The investigations reported in this paper were limited to members of the junior school who ranged in age from 11 to 14 years. The enrollment in the junior school was as follows:

Form	No. of Boys
I	23
II	34
III	39
—	—
Total I-III	96

The four boys previously mentioned, who had nephritis, were members of the second form.

Efforts were made to determine the incidence and the clinical features of illness in other members of the junior school. A review of the attendance records revealed that the number of students who were absent from their classrooms for at least one day per month increased sharply during February and March and declined again in April. As shown in table 1, the number of students who were absent from Forms II and III at some

TABLE 1

STUDENTS ABSENT FROM SCHOOL

Form	No. of Students Enrolled	Students Absent During							
		January		February		March		April	
		No.	%	No.	%	No.	%	No.	%
I	23	6	*26*	9	*39*	12	*52*	9	*39*
II	34	11	*32*	21	*62*	20	*59*	12	*35*
III	39	11	*28*	23	*59*	14	*36*	10	*26*

time during February was twice as high as in the preceding month and approximated 60% of the total enrollment. Chart 1 presents graphically the number of boys in each form who were absent on each school day during the period of study. Although it is evident that an increase in the number who were absent did occur among members of the junior school during February and March, it is also apparent that not many boys were absent at any one time. Moreover, excepting those with nephritis, not many boys were absent for more than a few days at a time.

With few exceptions the boys whose attendance was interrupted because of illness remained at home. The exceptions who were admitted to hospitals included the three boys mentioned, I.F., S.F. and R.O. who had nephritis and another boy, C.L., who had an ill-defined malady which began in mid-February and was suspected but not proved to be rheumatic fever. It will be recalled that one boy, H.K., whose illness also began in February, was treated for nephritis at home. Another boy, K.L., remained at home during the last two weeks in February because of an illness, initiated by fever, headache and generalized aches, which was diagnosed as influenza and later complicated by sinusitis. Still

another boy, S.R., also became ill in mid-February with listlessness, fever for two days, and sore throat. He remained in bed for about a week and then returned to school but lacked energy for a much longer period.

In other instances boys who remained at home because of illness did so for only a few days; they complained of "a cold" or "sore throat" and received medical attention, if at all, from their family physicians. It could not be established that any of the boys had scarlet fever. On the basis of the information that could be obtained from the parents, physicians and school authorities, no particular disease entity appeared to be prevalent among these boys and no distinctive features indicative of a common illness among them could be elicited in retrospect. Among the boys who were questioned and examined at the

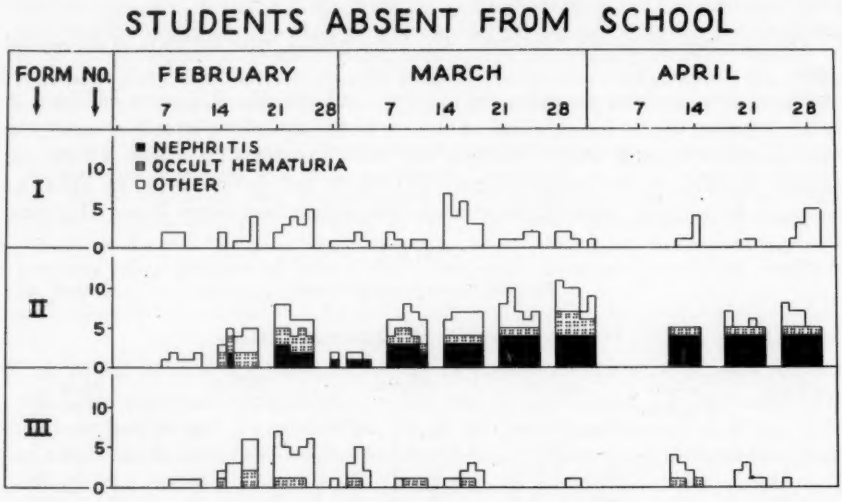

CHART 1

school only one, S.R., showed, at the time of examination, clinical evidence of active disease, in the form of acute pharyngitis on one occasion. These observations suggested that if an acute infection which led to the development of nephritis in four boys was widely prevalent among other members of the junior school, it must have been mild or inapparent in most of them.

RESULTS OF LABORATORY STUDIES

Urinanalyses: As shown in table 2, specimens of urine from 93 of the students in the junior school were examined, in all but one instance, at the time of the initial survey on March 31. None of the boys in the first form, but 12 in the second and nine in the third were found to have hematuria. The incidence of hematuria among those who had urinalyses done was 35% in the second form and 26% in the third form, making an over-all incidence of 23% among all students in the junior school, and 29% in members of the second and third forms which included all of the boys with recognized hematuria.

Urinanalyses were repeated with specimens obtained from 21 boys on April 11 following their spring vacation and from 16 boys on April 14. The additional specimens of urine were obtained, in most instances, from boys whose initial urinalysis was abnormal

and from those who were found to have hemolytic streptococci in cultures of the nasopharynx.

As shown in table 3, 16 boys were found to have hematuria at the time of the first urinalysis, in nine instances associated with definite albuminuria. On subsequent occasions five more boys, including one who had not had a previous examination, were found to have microscopic hematuria associated in three with concurrent or recent albuminuria. In 13 instances the second or third urinalysis revealed some evidence of improvement over the previous findings.

Based on the results of routine urinanalyses and the available clinical data, the 21 boys who were found to have hematuria were classified arbitrarily into three categories as indicated in table 3. Group 1 included the four boys with acute glomerular nephritis. In Group 2 were 12 boys who also had definitely abnormal urine on more than one occasion.

TABLE 2

INCIDENCE OF HEMATURIA

Form	No. of Students		
	Enrolled	Urine Examined	Found to Have Hematuria
I	23	21	0
II	34	34	12 (35%)*
III	39	38	9 (26%)*
Total	96	93	21 (23.%)

* Per cent of students whose urine was examined.

Some of them had an acute illness which, in no instances, however, was clinically recognizable as nephritis. Group 3 consisted of five boys who appeared to have minimal abnormalities of urine detected on one occasion; only one of these boys gave a history of recent illness and this did not resemble nephritis.

It is well known that microscopic hematuria may be detected by the technic of Addis even when the results of routine urinalysis are negative.[19] Addis counts of the RBC sedimented from urine were done on April 19 with specimens from each of 20 boys who had shown abnormal findings approximately 5 to 7 weeks earlier. These counts are recorded in table 3. It can be seen that the urinary excretion of RBC as determined by this method was still markedly elevated in each of the four boys in Group 1 even though they were all apparently recovering from nephritis. Ten boys in Group 2 and one in Group 3 were also found to have excessive hematuria as determined by this method. On the other hand, normal Addis counts were found with specimens of urine from one boy in Group 2 and from each of four boys in Group 3. From the standpoint of clinical disease and urinary abnormalities, it is evident that the findings in these three groups of students represent a gradient of diminishing severity. Although only the boys in Group 1 had obvious clinical features of nephritis, it seems apparent from the urinary finding that the students in Groups 2 and 3 also might be considered to have had nephritis in a clinically inapparent form.

Cultures for Hemolytic Streptococci: Because of the possible relation of hemolytic

TABLE 3

LABORATORY DATA ON STUDENTS WITH HEMATURIA

Student	Form	Urine*							Serum†		
		3/31/49		4/11/49		4/14/49		5/19/49 Addis Count RBC×1 million	Cultures of Nasopharynx for Hemolytic Strep.	4/14/49 Titer of Anti-Hyaluronidase	4/14/49 Titer of Anti-Streptolysin "O"	4/14/49 Titer of Anti-Streptokinase
		RBC	Alb.	RBC	Alb.	RBC	Alb.					
Group 1												
I.F.	II	+	+			0	0	87.0	Negative	1024	>600	0
S.F.	II	++	++	+	+	0	0	33.0	Negative	>4096	>500	125
R.O.	II	++++	++	+++	+++			450.0	Negative	>4096	>500	278
H.K.	II	+	+	+	0	+	0	150.0		2048	>600	417
Group 2												
S.R.	II	++	0			++	0	320.0	Positive	>4096	550	83
S.A.	II	+	+	0	++	0	0	0.0	Negative	64	50	25
C.L.	II	+	0			+	0	2.8	Negative	64	> 50	36
K.L.	II	+	+	+	+	0	++	1.0	Negative	128	250	36
R.S.	II	+	+			+	0	4.6	Negative	0	>500	278
P.A.	III	+	0	+	+	+	0	10.1	Negative	256		25
D.B.	III	0	+	+	++			7.0	Negative	64	100	36
H.G.	III	0	0	++	0	+	0					
E.L.	III	+	±	+	±			8.7	Negative	32	50	25
B.M.	III	+	+	+	++			2.0	Negative	64	100	36
P.M.	III	+	±	+	+	+	0	37.0	Negative	1024	450	>417
M.S.	III	+	+	+	++	0	0	8.0	Negative	2048		125
Group 3												
E.C.	II	0	0	+	+	0	0	21.0	Negative	2048	>500	>417
C.H.	II					+	0	0.5				
J.S.	II	+	0			0	0	0.0	Negative	16	150	36
D.R.	III	0	0	+	0			0.0	Positive			
T.C.	III	+	0			0	0	0.0	Positive			

* See under Materials and Methods for explanation of symbols.

† Titers expressed as reciprocal of serum dilution.

streptococci to the pathogenesis of acute nephritis, cultures of the nasopharynx were made from students in the junior school at the time of the first survey on March 31. Additional cultures were obtained on April 14, from boys who had hematuria and from those who were found to have hemolytic streptococci in the initial examination. All but two of the boys with hematuria were included among those who had cultures taken.

TABLE 4

INCIDENCE OF HEMOLYTIC STREPTOCOCCI IN CULTURES OF NASOPHARYNX

Form	No. of Students*		
	With Hematuria	Without Hematuria	Total
I	0	3/22	3/22
II	1/11	3/16	4/27
III	2/8	2/28	4/36
Total	3/19	8/66	11/85

* Expressed as a fraction in which the denominator indicates the number who had cultures done and the numerator the number whose cultures yielded hemolytic streptococci.

TABLE 5

IDENTIFICATION OF HEMOLYTIC STREPTOCOCCI FOUND IN CULTURES OF NASOPHARYNX

Source		Culture*	
Student	Form	3/31/49	4/14/49
D.C.	I	Pos.-?	
M.B.	I	A-12	
B.M.	I	C	
S.R.†	II	Neg.	A-12
J.C.	II	Pos.	Neg.
B.W.	II	Pos.	Neg.
W.	II	A-12	A-12
D.R.†	III	G	Pos.-?
T.C.†	III	A-?	Neg.
M.C.	III	Pos.	C
K.	III	Pos.-?	Neg.

* Pos. = Hemolytic streptococcus; Lancefield group and type not determined.
Pos.-? = Hemolytic streptococcus; efforts to determine group unsuccessful.
A-12 = Hemolytic streptococcus; Lancefield Group A, Type 12.
A-? = Hemolytic streptococcus; Lancefield Group A; efforts to determine type unsuccessful.
C = Hemolytic streptococcus; Lancefield Group C.
G = Hemolytic streptococcus; Lancefield Group G.
Neg. = No hemolytic streptococci found.
† Student with hematuria.

The results of this investigation are summarized in table 4. It can be seen that a total of 11 boys among the 85 who were cultured were found to harbor hemolytic streptococci. This represented an incidence of approximately 13%. The boys with positive cultures

included three in each of the first two forms and two in the third form. The distribution of positive cultures among boys with and without hematuria was not significantly different. The three boys with positive cultures among those who had hematuria are indicated in tables 3 and 5.

An attempt was made to classify the strains of hemolytic streptococci which were isolated from these patients into serologic groups and types according to the methods of Lancefield. As shown in table 5 at least five different serologic varieties of streptococci

TABLE 6

DISTRIBUTION OF STREPTOCOCCAL ANTI-ENZYME TITERS IN SERUM OF STUDENTS

Titers	Antistreptokinase		Antistreptolysin "O"		Antihyaluronidase	
	No. of Students		No. of Students		No. of Students	
	With Hematuria	Without Hematuria	With Hematuria	Without Hematuria	With Hematuria	Without Hematuria
0– 50	9	12	3	4	3	6
51– 100	1	3	2	2	4	3
101– 200	2	3	1		1	2
201– 300	2	1	1	4	1	4
301– 400				2		
401– 500	3	1	1	1		
501– 600			5	5		
601– 700			2			
1001–2000					2	1
2001–3000					3	2
4000					3	1
Totals	17	20	15	18	17	19
> 36*	8	8				
>159*			9	12		
>256*					8	4

* Approximate mean titer for healthy young adults.[20]

were represented among the 11 students with positive cultures. These included Group A, type 12; Group A, type undetermined; Group C, Group G, and at least one other category represented by three strains which did not belong to Group A, C or G. Strains of Group A, type 12, were recovered from three different students from the first and second forms, only one of whom, S.R., had hematuria. Strains of Group C streptococci were isolated from two different boys, one in the first, the other in the third form. An attempt was not made to classify the strains of streptococci isolated from three of the boys who did not have hematuria. These three strains may have belonged in categories previously identified or may have represented additional varieties. From the results of these investigations, a direct relation was not evident between the incidence of streptococci in cultures of the nasopharynx and the occurrence of hematuria among the boys studied. It should be

recognized, however, that the cultures may have been taken too late to detect the presence of organisms which were present at the time when the boys who developed nephritis first became ill.

Results of Serologic Tests: In a further effort to detect a possible relation between antecedent streptococcal infection and the occurrence of nephritis or occult hematuria quantitative determinations of antistreptokinase, antistreptolysin "O" and antihyaluronidase were made with specimens of serum obtained on April 14 from 17 of the boys with hematuria and from 20 members of the junior school who were not found to have hematuria. The titers in sera from the boys with hematuria are shown in table 3, and the distribution of titers in the sera of boys with and without hematuria is presented in table 6.

It can be seen from table 3 that the titers in sera from the four boys with nephritis included the highest encountered in this series although in serum from one of them no antistreptokinase was detected. Similarly, high titers of antistreptolysin "O" and antihyaluronidase but not antistreptokinase were also found in serum from another boy, S.R., whose second nasopharyngeal culture yielded hemolytic streptococci, Group A, type 12. Although elevated titers of the three different anti-enzymes frequently paralleled each other in individual specimens of serum, it is quite apparent that this was not invariably the case and that no obvious ratio existed between them. Among the boys with hematuria there appeared to be a trend toward a positive correlation between the Addis count and the serologic titers particularly of antistreptolysin "O" and antihyaluronidase.

From table 6, it can be seen that the distribution of titers in the serum of boys with and without hematuria was similar. The number of boys with titers in excess of approximate mean values for healthy young adults[20] was not significantly different in the two groups.

The higher titers which were observed in sera from certain representatives of both groups suggested that recent streptococcal infections might have been more prevalent among members of the junior school than was revealed by the bacteriologic findings. It should be pointed out, however, that the sera which were tested were obtained during "convalescence" from any antecedent infection, whether clinically apparent or not, which may have been responsible for the development of hematuria. As earlier specimens of serum were not available, it was not possible to determine the number of boys in whom the titers observed represented an increase over previous values. This is unfortunate in that a significant increment rather than any particular level of titer has generally been accepted as evidence of a related response. It was, therefore, impossible to ascertain from these serologic data either the individual boys or the total number who had recent streptococcal infection.

Comment

As pointed out earlier, the coincidental occurrence of acute nephritis in four adolescent boys who were classmates in the second form of a private day school appeared to be unusual and led to the investigations which have been described in this report.

Seventeen other boys who were members of the second and third forms of the school were also found to have red blood cells in their urine. The incidence of observed hematuria among members of these two classes was 29%, and it is quite possible that if more frequent urinalyses had been done, additional instances of hematuria might have been discovered. In most of these boys the condition which was responsible for the occurrence of red cells in their urine apparently persisted for weeks. This was indicated by the fact

that approximately three-fourths of the boys who had hematuria were found to excrete red cells in the urine on more than one occasion, and 15 of them had abnormally elevated Addis sediment counts from 5 to 7 weeks after the initial detection of red cells in their urine.

The investigations disclosed no unfavorable environmental factors which might have contributed to the occurrence of hematuria. Mild illnesses usually of short duration apparently became more prevalent among members of the junior division of the school during the middle of February 1949 at about the time when the four boys who developed nephritis had their initial symptoms. At no time, however, did there appear to be a local "outbreak" or "epidemic." A few of the illnesses were presumed on clinical evidence to be streptococcal but this was not confirmed by bacteriologic tests. The variations in severity, duration and features of illness in different members of the school were compatible, however, with the protean manifestations of streptococcal infections in this age group.[21] Infections with influenza A virus were present in the community at the same time[22] but were not detected in the school. Actually the cause of illness was not determined in any of the boys when they were ill and could only be surmised but not definitely established by retroactive evaluation.

The bacteriologic studies which were carried out in March and April disclosed that a total of 11 boys did in fact harbor hemolytic streptococci including three among 19 of those who had microscopic hematuria. The strains which were isolated, however, represented at least five different immunologic varieties and only four were in the Group A category.

The serologic tests for antistreptococcal antibodies revealed that practically all the boys whose sera were tested presumably had had some previous antigenic experience with streptococci, but the results did not indicate how recently the experience had occurred or disclose any significant differences between the boys who showed hematuria and those who were not found to have red cells in their urine.

It is probably arbitrary to say what degree of hematuria or assemblage of associated findings warrants a diagnosis of nephritis. It seems probable, however, that in the present study the differences in the clinical and laboratory features which were observed among the boys with hematuria represented variations in the manifestations of a disease common to all of them. It is obvious that many of the milder cases could easily have been overlooked. It does not follow, however, that the pathologic process in boys with clinically mild or inapparent disease was correspondingly less severe or that the prognosis was necessarily more favorable. It is quite possible that chronic glomerulonephritis, usually of obscure origin, may be initiated by episodes of this type.

SUMMARY

An outbreak of acute nephritis is reported which occurred among adolescent boys who were students at a private day school. Four boys in one class had clinically typical acute glomerular nephritis. Seventeen other members of this and one other class were found to have hematuria with or without associated albuminuria. The total incidence of hematuria among the 73 students in these two classes was 29%. Fifteen of the 21 boys with hematuria still had abnormally elevated Addis sediment counts approximately seven weeks after the initial examination.

Cultures of the nasopharynx were made from 85 students. Hemolytic streptococci were detected in 11 (13%) of the boys including three with hematuria. The results of attempts

to identify the streptococci by serologic technics indicated that at least five immunologically different varieties were represented.

Determinations of antihyaluronidase, antistreptolysin "O" and antistreptokinase in serum from 17 boys with hematuria and 20 without apparent hematuria revealed wide variations in titer but no significant differences between the two groups.

Clinical Histories

1. I.F., a 14 yr. old boy, developed a mild cold; it was characterized by sneezing and coughing, and subsided promptly. Two weeks later he had a sore throat for 1 day and fever of 37.8°C. He received penicillin by the oral route and returned to school in 3 days. Five days later he began to have swelling of the eyelids which was most noticeable in the morning. Four days later, when the facial edema appeared to be subsiding, swelling of the ankles was noted. His urine remained normal in appearance and quantity and he experienced no dysuria. Urinalysis, however, revealed the presence of albumin and red blood cells. A review of his past history and that of the family revealed nothing further that was contributory. He was admitted to the hospital the following day.

On physical examination he appeared to be obese, moderately ill, but in no distress. His temperature was 37.0°C., pulse 80, and respirations 16. The blood pressure was 184/120 mm.Hg. in his right arm and 175/110 mm.Hg in the left. No edema of the face was noted, and the eye grounds appeared normal. The ears, nose and throat were not remarkable. Examination of the heart revealed a diffuse apical impulse. The left border of cardiac dulness was just outside of the midclavicular line. The sounds were of good quality and no murmurs were heard. Palpation of the abdomen disclosed some resistance in the right upper quadrant; other abdominal findings were not remarkable. Pitting edema was present over the dorsum of both feet; the legs also felt edematous but no pitting was noted.

The initial laboratory findings included RBC count 4.5 million/cmm., Hgb. 13.5 gm./100 cc. and WBC count 12.9 thousand/cmm. of which 71% were polymorphonuclear. The urinalysis showed a specific gravity of 1.027, and albumin 3+. Occasional white blood cells but no casts or red blood cells were found in the sediment. On subsequent urinalyses, albumin, white blood cells and occasional red blood cells were detected for about 2 wk. Subsequently the urine gradually became clear. Cultures of the nose and throat yielded no hemolytic streptococci or other obvious pathogens. Chemical determinations with blood were within normal limits; NPN was 34 mg./100 cc. The venous pressure was 16.5 cm. Roentgen examinations of the heart and lungs were normal; films of the sinuses revealed evidence of left maxillary sinusitis and thickening of the right antrum.

The patient was kept in bed and given a salt-free diet. Because of the elevated venous pressure, he was treated with digitalis for 8 days. Except for occasional elevations to 38.3°C. during the second week, he remained afebrile while in the hospital. After the first week his blood pressure remained normal. The edema disappeared. He appeared to have recovered and to have normal cardiac and urinary findings at the time of discharge from the hospital 1 mo. after admission.

2. S.F., a 14 yr. old boy, became ill with sore throat, stuffy nose, slight cough and fever to 38.3°C. He was treated with aspirin and 2 days later returned to school. Five days later he had a chill accompanied by generalized aches and a fever of 38.8°C. The following day his temperature rose to 40.5°C. and he was given an injection of penicillin. Treatment was continued with penicillin 100,000 units p.o. 5 times/day. Three days later he became drowsy, had loss of appetite, and developed puffiness of the face. Two days later he began to vomit and complain of headache and pain in the knees. Urinalysis revealed the presence of albumin. Nothing in his past or family history appeared to be contributory. He was admitted to the hospital.

Physical examination revealed a well-nourished and well-developed boy who appeared moderately and acutely ill. His temperature was 37.1°C., pulse 80, respirations 24, blood pressure 152/100 mm.Hg. The face was slightly puffy, but no peripheral edema was noted. A soft systolic murmur was heard over the precordium. The eye-grounds were normal and other findings on physical examination were not remarkable. The heart did not appear to be enlarged.

The initial urine examination revealed a specific gravity of 1.010, albumin 3+, and 5 to 10 leucocytes and red blood cells/hpf in the unspun sediment. Subsequent urinalyses showed an increase in the specific gravity to 1.022, and a gradual disappearance of albumin by the time of discharge. The cellular elements had disappeared by 1 wk. after admission, NPN was 49 mg./100 cc. at the

time of admission and on 2 subsequent occasions 40 and 47 mg./100 cc. Roentgen examination of the chest revealed no evidence of cardiac enlargement, but there was a thin area of density in both costophrenic angles possibly representing a minimal amount of plural thickening or fluid.

The patient was treated with a low salt diet and bed rest. His course was uneventful. The hypertension and the edema disappeared, and the urine became clear. At the time of discharge 1 wk. after admission there was a soft precordial systolic murmur still present and the blood pressure was 120/84 mm.Hg.

3. R.O., a 13 yr. old boy, developed a cold and sore throat accompanied by an elevation of temperature to 38.3°C. After 1 wk. of rest at home, he returned to school apparently well. Four days later, however, he felt tired and the following day passed grossly bloody urine. A review of his past and family history revealed no additional data that was relevant. He was admitted to the hospital 2 days later.

Physical examination revealed a well-developed and nourished boy who appeared pale but not otherwise ill. His temperature was 37.2°C., pulse 100, respirations 18 and blood pressure 130/88 mm.Hg. The margins of the optic discs in both eyes appeared hazy. The tonsils were slightly enlarged and the pharynx was hyperemic. The heart sounds were of fair quality and a questionable systolic murmur was noted. No edema was observed.

The initial urine specimen appeared red and had a specific gravity of 1010; albumin was 3+ and the sediment contained many red and white blood cells as well as granular and cellular casts. The results of examinations of the blood were as follows: NPN 46.5 mg./100 cc.; cholesterol 173 mg./100 cc.; WBC count 12.3 thousand/cmm. with 67% polymorphonuclear; Hgb. 10.0 gm./100 cc. and RBC count 3.0 million/cmm. Throughout the period of hospitalization, tests of the urine revealed the presence of albumin (trace to 2+), and varying numbers of red cells, leucocytes and casts. The specific gravity ranged from 1.010 to 1.015. NPN content of the blood increased to a maximum of 110 mg./100 cc. on the 7th hospital day and thereafter declined to 26 mg./100 cc. at the time of discharge. Cultures of the nose and throat on 2 occasions yielded no pathogens and a culture of the urine was sterile. An electrocardiogram revealed A-V nodal rhythm on the 2nd hospital day but subsequent records were interpreted as normal. Chest RG revealed no enlargement of the cardiac shadow.

The patient was given a high caloric, low salt diet with no restriction of fluids. His daily urinary output ranged from 200 to 600 cc. for the 1st 5 days and thereafter ranged from 1250 to 1650 cc. The blood pressure was stable during the first few days in the hospital but rose to 166/104 on the 10th day at a time when the NPN was 110 mg./100 cc. and there was obvious edema of the face and extremities. The patient appeared acutely and seriously ill, but subsequently improved. The edema disappeared, the blood pressure and NPN returned to normal. At the time of discharge from the hospital after 24 days, urinanalysis still showed a specific gravity of 1.015, 2+ albumin, many WBC and a few RBC.

4. H.K., 13 yr. of age, suddenly had a rise in temperature to 39.6°C. associated with the onset of headache and sore throat. Examination at that time revealed bright red inflammation of the pharynx with angina and tenderness but not swelling of the cervical lymph nodes. The family history was not remarkable. The boy was treated with sulfadiazine for a period of 5 days; his temperature returned to normal in 2 days.

Four days later fever recurred, and again he was found to have hyperemia of the pharynx and tenderness of the cervical lymph nodes. Six days later edema of the face was noted, particularly of the eyelids. His blood pressure was 130/0 mm.Hg. Urinalysis revealed normal color, a specific gravity of 1020 and albumin 3+. The sediment showed occasional hyaline and granular casts, occasional red blood cells and 25 to 40 white blood cells/high dry field. Examination of the blood revealed RBC count 4.6 million/cmm. and WBC count of 11.9 thousand/cmm. with 67% polymorphonuclears. NPN was 53.5 mg./100 cc. 9 days later and 30.5 mg./100 cc. 3 days after that. Urinalyses on the 17th, 24th and 27th days of illness revealed the continued presence of albumin, casts, red cells and leucocytes. Subsequent examinations showed progressive clearing. This boy was treated at home and remained in bed for over a month. He had apparently recovered when he returned to school a few weeks after the rest at home.

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SPANISH ABSTRACT

Brote Epidémico de Nefritis Aguda en Adolescentes Escolares

Se reporta una epidemia de nefritis aguda ocurrida en escolares adolescentes varones que atendían a una escuela privada durante el día. Cuatro estudiantes de la misma aula presentaron el cuadro clínico típico de una nefritis glomerular aguda. Otros diez y siete estudiantes pertenecientes a aulas distintas presentaron una hematuria con o sin albuminuria asociada. La incidencia total de hematuria entre 73 estudiantes fué de 29%. De 21 pacientes con hematuria 15 continuaban presentando conteos elevados de Addis del sedimento urinario aproximadamente siete semanas siguientes el examen inicial.

Se demostró la presencia del Estreptococo hemolítico en los cultivos de la nasofaringe de 11 estudiantes (13%) de un grupo de 85, incluyendo tres casos con hematuria. Los resultados obtenidos con la técnica de identificación serológica indicaron que por lo menos cinco variedades inmunológicas distintas de estreptococos estuvieron representadas en este brote epidémico.

La determinación de las concentraciones del suero de anti-hialuronidase, anti-estreptolisina "O" y anti-estreptokinasa en 17 casos con hematuria y en 20 casos sin hematuria demostraron variaciones grandes en los títulos aunque sin diferencias significativas entre los dos grupos.

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LABORATORY ASPECTS OF ANTIBIOTIC THERAPY

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THE development of antibiotic therapy has had a profound effect upon the function and usefulness of the bacteriology laboratory. For a year or two after the introduction of penicillin many clinicians believed that culture studies were no longer needed; as a result the number of specimens submitted to the laboratory declined sharply. But the appearance of streptomycin reversed this trend, and the subsequent discoveries of chloramphenicol, aureomycin and terramycin have created a need for culture study which greatly exceeds the level existing before the days of penicillin. The purpose of the present paper is to explain why this is so and to evaluate the methods available for the laboratory control of antibiotic therapy.

The vast majority of mild infections do not need bacteriologic studies. Routine administration of penicillin is effective against most of the gram-positive and gram-negative cocci so often responsible for infections above the diaphragm. And empiric use of aureomycin, chloramphenicol or terramycin generally cures those due to gram-negative bacilli. However, there remains a residue of cases successful treatment of which requires microbiologic guidance. Among these are severe acute infections in which spontaneous recovery is unlikely and purely empiric therapy risky. Failure of a drug to produce clinical improvement in 72 hours probably indicates that the causative organism is resistant to that drug.[1] Therefore, refractory infections, both acute and chronic, deserve bacteriologic investigation, as also do those which relapse or change in character in such a manner as to suggest alteration in bacterial flora. The reader is referred to the excellent article by Jawetz and Marshall for specific illustrations of this point.[2]

Prior to the advent of antibiotics the primary function of the infectious disease laboratory was to isolate and identify the causative organism. At the present time, however, identification of the isolates is not enough. Although it is necessary to establish the presence of significant bacterial types, this information is of minor interest only. The important question is: Which of the available antibiotics is most likely to be effective? Because a practical method is available for determining in vitro susceptibility to antibiotics, this has become the principal contribution of the laboratory to the management of infectious diseases.

As long as penicillin was the only antibiotic, there was little need for in vitro susceptibility tests. But there are now six or more of these drugs, some of which have almost identical antibacterial spectra. This fact has created a major problem for the clinician. How can he decide which one to use? Although cost, lack of side reactions and ease of administration must necessarily influence this choice, the determining factor is—or should be—the susceptibility of the causative organism to the several drugs.

Aside from clinical trial and error, the only way to select the proper antibiotic is through the use of in vitro tests. The common practice of choosing the antibiotic on the

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basis of culture and species identification is inadequate. Not all streptococci are susceptible to penicillin nor all coliform bacilli to the newer antibiotics. More than half the staphylococci isolated from hospitalized patients are resistant to penicillin.[3] Although various coliform bacilli are commonly listed among the species susceptible to aureomycin, chloramphenicol and terramycin, strains resistant to one or more of these drugs are frequently encountered. Furthermore, the incidence of resistant strains is increasing. Whereas the proportion of penicillin-resistant staphylococci in 1944 was about 14%,[4] it is now nearly 60%.[3] And it is possible that other bacterial species are also becoming more resistant to penicillin.[5] The appearance of resistant strains has been most pronounced in the case of streptomycin, the usefulness of which is now limited almost entirely to the treatment of tuberculosis. It is too soon to predict the rate at which bacteria will become resistant to the newer antibiotics, but recent reports[6,7] suggest that the proportion will increase with time. None of the antibiotics in general use is effective against the majority of Pseudomonas organisms. Yet specific strains may be very susceptible to one of the drugs as the following incident illustrates. Four successive isolations of Pseudomonas made in the author's laboratory were tested against six antibiotics. Each strain was inhibited by a low concentration of one of the antibiotics, but in each instance it was a different one. Incidentally, clinical experience corroborated the laboratory findings with these four strains. Clearly then, assumption of antibiotic susceptibility based solely upon species identification is impossible because within any given species strains vary widely and in a highly specific manner.

Susceptibility to antibiotics is relative. Group A streptococci and pneumococci are generally susceptible to a concentration of less than 0.1 μg./cc. penicillin. These organisms succumb to relatively small doses. Streptococci of the intestinal type (enterococci), on the other hand, often require concentrations of 5 to 10 μg./cc. Yet the latter are still susceptible since blood levels of that order can be attained in vivo by the use of daily doses of several million μg. as has been demonstrated by Loewe[8] and others in the successful treatment of subacute bacterial endocarditis. Susceptibility to the newer antibiotics is also relative. Therefore, it is important from a therapeutic standpoint to know whether any given organism is very susceptible, moderately susceptible, slightly susceptible or resistant. Since the in vitro tests in current use provide adequately quantitative results, they constitute an invaluable guide to adequate dosage in the treatment of refractory infections.

Antibiotic susceptibility tests are practical and well within the scope of any bacteriology laboratory capable of doing cultures. The technic developed in this laboratory for routine use[9] is carried out on the primary isolation plate, thereby avoiding any delay beyond that required for routine incubation of the culture. A filter paper disk is immersed in a standard antibiotic solution and immediately placed upon the surface of a freshly inoculated blood agar plate. Four or five different antibiotics can be tested simultaneously. After overnight incubation of the culture, susceptibility is visualized as a zone of inhibition surrounding the disk (Fig. 1). The size of this zone is a measure of the relative susceptibility which under standard conditions may be translated ($\pm$ 25% error) into specific μg./cc. values.[9]

This technic, or some modification of it, is widely used at the present time and has been extended to include all the newer antibiotics.[10] The principal disadvantage of the original procedure is the necessity of preparing accurate standard antibiotic solutions, a step which is not only time-consuming but also requires considerable knowledge of the physical properties of the various drugs. This disadvantage has now been overcome by the intro-

duction of dried antibiotic disks* or tablets† as commercial items. The author's associates have tested these preparations and find them quite acceptable. The results indicate, however, that it is not necessary to use all three concentrations of bacto-sensitivity disks ® as recommended by Difco; the intermediate set appears to be adequate. Similarly, the author is inclined to omit the stronger concentration tablet sold by Boyle & Co. and by Commercial Solvents Corp. The commercial dried disks and tablets are particularly suited

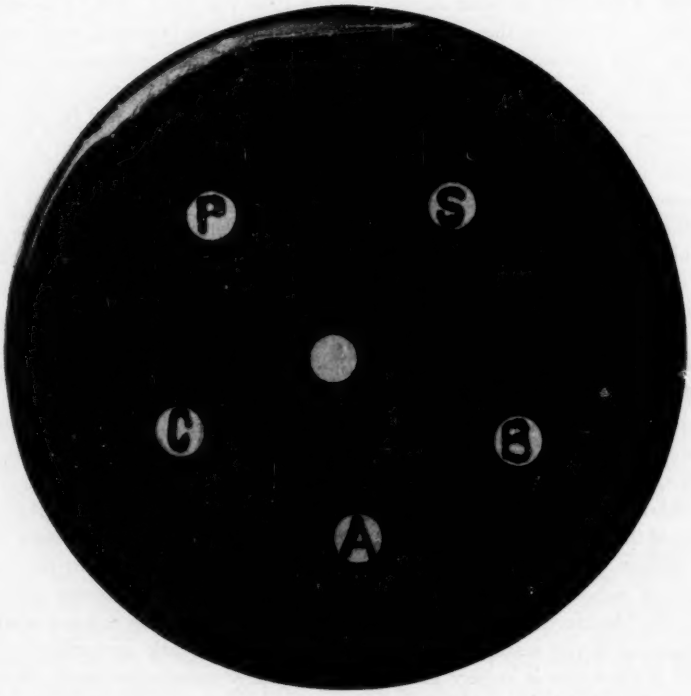

FIG. 1. Staphylococcus in pure culture. Very susceptible to penicillin (P), moderately susceptible to dihydrostreptomycin (S), bacitracin (B), aureomycin (A) and chloramphenicol (C). Center disk is control. (Courtesy, Dr. T. G. Anderson.)

to the needs of the small hospital and have removed the last obstacle to the routine application of this method.

The presence of mixed bacterial types in primary culture does not complicate susceptibility determinations. Technicians in this laboratory have no difficulty in identifying 2 to 4 pathogens on the same blood agar plate and in estimating their respective susceptibilities to five different antibiotics (Fig. 2). On the contrary, selective action of the several drugs frequently permits detection of organisms such as H. influenzae which otherwise would be obscured by overgrowth of hardier types.

The disk technic does not yield precise results since the number of bacteria in the

* Difco Laboratories, Detroit.

† Boyle & Co., Los Angeles 33. Lederle Laboratories, New York (aureomycin only). Commercial Solvents Corp., Pharmaceutical Division, 17 E. 42nd St., New York.

culture is an uncontrolled variable which influences zone size. Nevertheless, it does permit classification of the test organism as: (a) very susceptible; (b) moderately susceptible; (c) slightly susceptible; (d) resistant. Although crude, this method appears to be adequate for practical purposes. If desired, the technic can be standardized under the conditions existing in any one laboratory;[9] this will permit direct translantion of zone size to units or μg./cc.

Evaluation of Susceptibility Tests

The results of in vitro tests correlate well with clinical experience. Providing the causative organism is actually isolated and is found susceptible, the antibiotic so selected

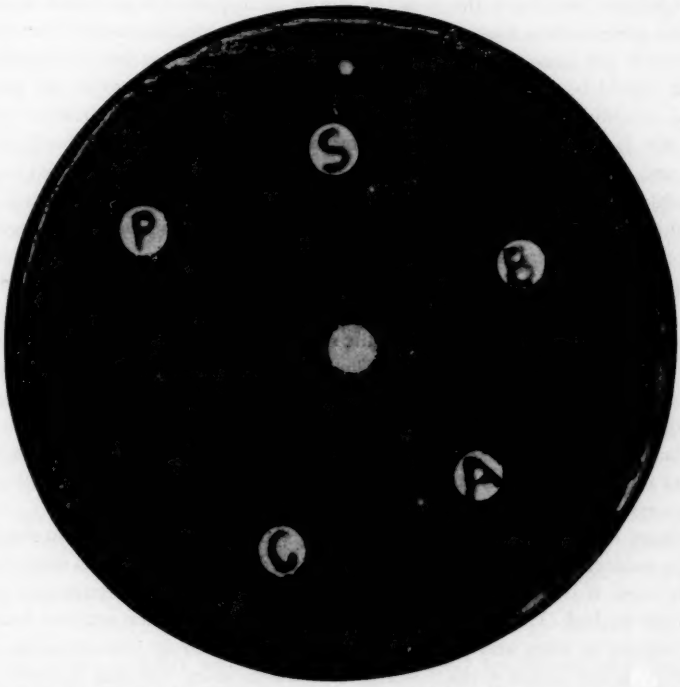

Fig. 2. Nasopharyngeal culture containing coagulase-positive staphylococcus (large colony) and Group A streptococcus (small colony). Staphylococcus is very susceptible to dihydrostreptomycin and aureomycin, moderately so to bacitracin, slightly so to chloramphenicol and resistant to penicillin. Streptococcus is very susceptible to aureomycin, moderately so to penicillin and dihydrostreptomycin, slightly to bacitracin and chloramphenicol. Aureomycin is drug of choice. (Courtesy, Dr. T. G. Anderson.)

can be expected to prove effective therapeutically. The truth of this statement is most clearly established in cases which have already been treated for some time without improvement. Our common experience in such instances is to find the etiologic organism quite resistant to the antibiotic previously used and to note satisfactory response upon administration of the drug selected on the basis of susceptibility tests. Another situation which illustrates the value of in vitro tests is the case which relapses after apparent

improvement, especially with a change in the nature of the disease process. The locus of infection is often an area accessible to secondary bacterial invasion, such as the throat, bronchi, surgical wounds, so that actually one is dealing with a mixed flora. Among these may be streptococci which are the primary incitants and which respond readily to penicillin. In a few days, however, gram-negative bacilli previously held in check by the antagonistic action of streptococci and other penicillin-susceptible bacteria now grow out unchecked and produce their own type of disease. Susceptibility tests made at this time will readily reveal the circumstances and suggest the proper therapeutic approach.

It would be too much to expect the in vitro-in vivo correlation to be perfect. Even when the tests are carefully made, one sees cases which fail to respond according to in vitro predictions. No doubt this is often due to inadequate dosage. There may also be mechanical and anatomic barriers which prevent drug penetration to the infected area, as in walled-off abscesses and subacute bacterial endocarditis. In such circumstances the organism should be considered less susceptible than it appears in vitro and the dosage increased accordingly. Perhaps the most important reason for discrepancies with penicillin is the fact that the disk test measures only the ability of an antibiotic to inhibit growth and not the bactericidal power. Unlike most antibiotics, penicillin is rapidly bactericidal for some bacteria in concentrations easily obtained in the tissues. But the relationship between the static and cidal concentrations is highly variable, ranging from 2 to 20 fold. Therefore, if, as Eagle believes,[11] the therapeutic efficacy of penicillin is due to its direct killing effect, laboratory tests should measure bactericidal action. At the present time, however, there is no routine method for doing this. It should be emphasized that these remarks do not apply to aureomycin, chloramphenicol or terramycin which have no appreciable bactericidal action. There are undoubtedly other factors which must be understood in order to explain discrepancies, such as those mentioned by Long et al.[12] regarding aureomycin and chloramphenicol. In general, however, therapeutic failures appear to be uncommon if the drug employed is shown to be active in vitro and consideration is given to anatomic barriers and other factors which may prevent adequate tissue concentrations.

Sometimes, the reverse event occurs. Bacteria resistant to penicillin in vitro respond well in vivo as evidenced by prompt clinical recovery. Ordinarily this happens only when large doses are used. It is difficult to obtain reliable data on high concentrations of penicillin by the disk method. Therefore, certain organisms, especially gram-negative bacilli, may appear resistant in vitro and yet be satisfactorily controlled by administration of large doses of penicillin. Another point worthy of mention is the fact that infections in general are overcome by the combined action of drug and the body's immunologic mechanisms, particularly phagocytosis. A patient whose phagocytic powers are great may easily dispose of the relatively few resistant or drug-inhibited bacteria which survive exposure to antibiotics, whereas another individual's defense mechanisms may be inadequate. In any event, in vitro tests do not include the immunologic factor which always operates in favor of the patient. Therefore, antibiotics in general, and penicillin in particular, may often be employed successfully in the treatment of infections due to bacteria which appear to be resistant in vitro.

The true value of combination antibiotic therapy is not clear at the moment. In the test tube, four different effects may be observed when bacteria are exposed to a combination of two drugs; i.e., synergism, additive action, no effect or antagonism.[13] Although definite drug antagonism has been demonstrated in experimental infections,[14] this phenomenon has not yet been reported in human infections. Addition of an anti-

biotic which is without in vitro activity to another which by itself is fairly effective does not increase antibacterial activity. On the other hand, the additive action of two antibiotics may be observed both in the test tube and in the patient. Addition to the therapeutic regimen of a second antibiotic known to be active in vitro often results in clinical improvement of a refractory infection.[2] Combined therapy has its greatest application in the treatment of infections due to relatively resistant organisms,[15] probably by retarding or preventing the development of resistant mutants. This is probably the mechanism of synergism, or the potentiation of one drug by another, which is sometimes observed in vitro and in experimental infections. Furthermore, it has been shown that relatively resistant organisms may be killed in vitro by a combination of drugs which separately are only bacteriostatic.[16] Although the future of combination antibiotic therapy is uncertain, it is already evident that the laboratory can contribute in this field by developing practical methods for testing combinations of antibiotics for clinical use.

Discussion

This paper from necessity is limited to the subject of bacterial infections. There is no practical laboratory method for determining the antibiotic susceptibility of viruses. Tests with fungi are done as easily as with bacteria and in the same manner, but only the actinomyces are susceptible to the antibiotics now available. No mention has been made here of bacteria which are ordinarily isolated on media other than blood agar, e.g., enteric pathogens and the tubercle bacillus. Susceptibility tests on these organisms are made with pure cultures. Enteric bacilli may be tested by the disk method. But the tubercle bacillus is inoculated into a series of tubes containing media in which the drug under test has been incorporated.

It seems safe to predict that the microbiologic laboratory is destined to play an expanding role in the management of infectious diseases. As the number of antibiotics increases, the problem of selecting the best antibiotic for a refractory or relapsing case promises to become more complex. The clinician who in the past has not had access to a bacteriology laboratory will find a greater need for one. Therefore, it appears inevitable that small community hospitals which do not now have a bacteriologic technician must soon acquire one. Failure to do so will result in tremendous wastage and widespread abuse of antibiotics.

Summary

Bacterial strains within a single species exhibit highly specific susceptibility patterns when tested with the several antibiotics currently available. Because in vitro susceptibility tests constitute the only certain method for predicting clinical response, the bacteriology laboratory is playing an expanding part in the choice and control of antibiotic therapy. Although there is no need for bacteriologic studies in the vast majority of infections, they are sometimes essential to the successful management of severe acute, refractory and relapsing infections. The correlation between laboratory and clinical results is good providing allowances are made for certain factors discussed in this paper. Antibiotic susceptibility tests are entirely practical and should be used routinely in all laboratories which do bacterial cultures.

Acknowledgment

The writer has drawn freely from the experience of his associate, Dr. T. G. Anderson, in the preparation of this manuscript and wishes to express his gratitude for permission to use unpublished material.

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Spanish Abstract

Aspectos del Laboratorio en la Terapeutica Antibiotica

El autor señala que a los pocos años siguiente a la introducción de la penicilina, muchos clinicos creyeron unnecesarios el uso de cultivos de bacterias; debido a esto el número de exámenes remitidos al laboratorio declinó notablemente. La introducción de la estreptomicina, aureomicina, terramicina y cloromicetina, cambió radicalmente este concepto creando una mayor necesidad para los cultivos de bacterias, los cuales exceden grandemente a las demandas existentes antes de la introducción de la penicilina.

Antes del advenimiento de los antibioticos, la función primaria de los laboratorios de enfermedades infecciosas consistian en la identificación del agente etiologico. Actualmente, sin embargo, la contribución principal del laboratorio consiste en la determinación de la susceptibilidad "in vitro" de la bacteria a los distintos antibioticos.

Variedades de bacteria dentro de una misma especie exiben caracteristicas especificas de susceptibilidad cuando son sometidas a la acción de los distintos antibioticos en uso. Debido a que las pruebas de susceptibilidad en vitro constituyen el único medio cierto de pronosticar la repuesta clínica, los laboratorios bacteriologicos juegan un papel importante en la selección y control de la terapeutica antibiotica. A pesar que no haya necesidad de estudios bacteriologicos en la gran mayoria de las infecciones, a veces estos cultivos son esenciales para el manejo eficiente de enfermedades agudas severas, é infecciones refractorias. En general la correlación entre el laboratorio y los resultados clinicos es excelente. Se estima, que las pruebas de susceptibilidad antibiotica son enteramente practicas y deben usarse rutinariamente en todos los laboratorios bacteriologicos.

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EARLY INTEREST IN PEDIATRICS IN SOUTH CAROLINA

By Joseph Ioor Waring, M.D.
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FROM the few existing accounts of the development of pediatrics in America one gets the impression that there was little or no recorded concern for the subject before the early part of the nineteenth century. Garrison[1] mentions Thomas Thacher's "Brief Rule" (1677-78), Samuel Bard's paper on "Angina Suffocativa" (1771), Benjamin Rush's writings on the Cholera Infantum (1773) and Hezekiah Beardsley's paper on Pyloric Stenosis (1788) as the only writings of pediatric interest which were published before 1800. Adams[2] previously had considered Rush as one of the first in this country to write on pediatric subjects, counting Rush's "Account of the Influenza, as it appeared in Philadelphia in the Autumn of 1789, the Spring of 1790, and the Winter of 1791" as a contribution to the clinical description of the disease in children, and crediting Charles Caldwell's thesis written in 1796 at the University of Pennsylvania on "An Attempt to Establish the Original Sameness of Three Phenomena of Fever (principally confined to infants and children) described by medical writers under the several names of Hydrocephalus Internus, Cynanche Trachealis and Diarrhea Infantum" with being the first truly pediatric publication in this country. With such scanty background for our enormous pediatric literature of the present, it might not be amiss to note some few writings which came out of Charleston in the 18th and early part of the 19th centuries, and, without trying to squeeze too much blood out of a turnip, to show that there was some written evidence of interest in pediatrics which was perhaps somewhat more localized in South Carolina than in any other parts of the country.

In 1738 the question of inoculation against the prevailing smallpox was a matter of acute concern in Charleston. Popular arguments for and against the practice were lively, as were the discussions among the doctors as to the preferable method. James Killpatrick,[3] one of the chief proponents of inoculation, performed the operation on an infant who was so unfortunate as to die after the event. Being subjected to much criticism, Killpatrick published in September 1738 a pamphlet which was entitled "The Case of Miss Mary Roche, who was inoculated June 28, 1738, etc.," and was printed by Lewis Timothy, publisher of the South Carolina Gazette.[4] Although no copy of the original seems to be extant, Killpatrick refers to the appearance of this pamphlet in a later publication of his[5] and describes the circumstances of the case as follows:

"Miss Roche was about ten months old, a very hale plump child, and a hoarse pipe for an infant. I was consulted about her inoculation, and advised deferring it till the fall, if they thought she could be preserved from infection in the meantime. The parents doubting this, and, being urged by my colleague, Thomas Dale, M.D., to inoculate her at all events, it was performed the 28th of June. She sickened the 6th of July following, in a violent manner, took a little puke, which operated four times, and a glyster which produced one free stool, after 48 hours costiveness. She was very tense and hot all night; it was impossible to open a vein: She took a drachm and half of Diacodium, and had it repeated in better than an hour, which abated her fever and tension a little; but next morning everything was exasperated, and she expired suddenly in convulsions."

(Received for publication Feb. 27, 1951.)

This pamphlet drew the fire of Dr. Dale, Killpatrick's critic, and soon there was announced the impending publication of "The Case of Miss Mary Roche, more fairly related and etc., by Thomas Dale, M.D.,"[6] and later[7] again the proposed appearance of two other counterblasts. Whether these reached the dignity of print is not recorded.

Thus it might be claimed that Miss Mary Roche was the first infant of the country to achieve the distinction of recorded pediatric interest.

The next pediatric record is that of a harlequin fetus, appearing in a diary by the Rev. Oliver Hart, A.M., pastor of the Baptist church in Charleston:

"On Thursday, April ye 5th, 1750, I went to see a most deplorable object of a child, born the night before, of one Mary Evans, in Chas:town. It was surprising to all who beheld it, and I scarcely know how to describe it. The skin was dry and hard, and seemed to be cracked in many places, somewhat resembling the Scales of a Fish. The Mouth was large and round, and wide open. It had no external nose, but two Holes where the Nose would have been. The Eyes appeared to be lumps of coagulated Blood, turned out, about the Bigness of a Plumb, ghastly to behold. It had no external Ears, but holes where the Ears should be. The Hands and Feet Appeared to be swoln, were crumpt up, & felt quite hard. The back part of its Head was much open. It made a strange kind of a noise, very low, which I cannot describe. It lived about eight and forty hours, and was alive when I saw it."[8]

Just after the publication of Rush,[9] concerning the cholera infantum, there appeared a treatise by Lionel Chalmers[10] of Charleston, who also wrote of the intestinal disorders which he had observed. Indeed Rush refers to the fact that "It is distinguished in Charleston, in South Carolina, by the name of 'the April and May disease,' from making its first appearance in these two months."

Chalmers' two volumes of 446 pages covered many subjects, and some 50 pages are concerned with diseases rather purely pediatric, e.g., "Of the Disorders to which Children are liable at this Season"; "Of Worms in Children"; "Of Convulsions in Children"; "Of the Thrush"; "Of the Runnings from behind the Ears of Children, and other cutaneous Disorders"; "Of the Suffocating or Catarrhal Peripneumony in Children"; "Of Nervous Asthma or Suffocatio Stridula in Children"; "Of the Hooping-Cough."

Some of Chalmers' advice is not too far from the modern:

"If the stools are large and watery, every thing that is purgative must be abstained from; but rhubarb, either toasted or plain, may be given in small doses as a stiptick, together with crabs eyes or calcined hartshorn, made as warm with spiritus volatiles oleosus, oil of cinamon or mint, as the child can bear it; for an exceedingly great loss of strength presently ensues from this disorder. The vehicle of these medicines, ought to be a decoction of cinamon, or of any gently austere vegetable, that is not nauseous to the taste, in order to constringe the overdilated and weak vessels within, that a further wasteful effusion of their contents may be prevented. . . .

"Various means have been proposed for destroying worms; but the best disappointed us at times, and on other occasions those creatures will come away as it were of their own accord; or this might happen, after the person had taken some insignificant thing or other, which thenceforward acquires the character of a vermifuge. . . .

"I have oftentimes observed, that children are most commonly seized with convulsions in fevers during sleep, owing, probably, to the terrifying dreams which people are liable to at those times, from the unnatural excitations of the common sensory, together with the plethorick condition of the vessels in the brain. . . .

"The convulsions, however continue sometimes so long, or the stupor may be so great, as to make it necessary, to hold volatiles often to the nose; to take some blood either from the jugular or foot; to put the patient in warm water as deep as his waist for some minutes; and being then quickly wiped dry with a hot cloth, warm bricks should be laid on each side of the ancles. . . .

"This disease (whooping cough), commonly begins with a frequent but dry cough; nor have the patients that running at the nose, snuffling or hoarseness, which often ensue from catching cold. The coughing by degrees holds longer, and becomes so severe in a few days, that the sick scarcely have time to breath during the fits. For so spasmodically affected are the lungs and their appendages, that one interrupted act of violent expiration continues, till the patient, being ready to be stifled, is obliged to fetch breath with all his might, in spite of the convulsed condition of these organs. . . ."

Some time before the appearance of Chalmers' book, a Charlestonian who was a student at Edinburgh had produced as a graduation thesis (in Latin)[11] a rather considerable brief text on pediatrics, or more properly, on "the prevention and cure of diseases of infants." The preventive phase of pediatrics had received rather scanty attention before this time (1773), and the emphasis which George Logan put on the aspect of his subject is worthy of some note. There is rather much of Cadogan and probably other writers in the thesis, but the author's emphasis on certain thoughts is quite apt throughout the 44 pages of his dissertation, from which the gist may be lifted somewhat as follows:

Infancy is tiresome and long, and little has been written of the diseases which afflict it. Children would be in better health if they were not coddled. The doctors' duty is not only to cure, but to prevent. For this purpose, infants should be inured to cold and fresh air, should be clothed lightly and loosely, without shoes or stockings, and their clothing should be changed frequently.

Maternal breast feeding is best, and the infant should be fed shortly after birth in order to get the beneficial effect of the colostrum. Healthy nurses are essential. The baby will take what he wants from the breast, and any excess is vomited harmlessly. If the mother cannot nurse, use of a wet nurse is far better than artificial feeding.

Spontaneous exercise by the child is very desirable, and bouncing is a help. When he is about 9 months old "according to his strength let him creep or walk as much as he pleases." No artificial aids should be used. "Their obvious desire to touch everything, to investigate everything . . . should be wisely cherished."

Keep children out of crowded and stuffy rooms, and bathe them at least once a day.

Besides the contagious diseases, the diseases to which infants are prone are thrush, hydrocephalus, rickets and teething. Thrush is idiopathic in infants, often accompanied by convulsions, and due to bad foods or unhealthy nurses. Various drastic treatments are used, and the mouth may be painted with white vitriol (zinc sulfate). Hydrocephalus is described in the terms used by Robert Whytt of Edinburgh. Rickets is congenital, and ancient in its history. It may be due to excess of acidity or dirt. Since rachitic infants teethe late, the disease is closely connected with some defect in the formation of the bones—"a lack of nourishment, arising from weakness of the assimulating organs." Peruvian bark is the best tonic for it.

Teething is not a disease. Teething rings are harmful. Blood-letting may help.

George Logan made no great pediatric contribution, unless it was to stimulate some interest in the simpler preventive measures, but he must have brought back to Charleston

a concern for the pediatric element in his active practice. He was born near Charleston in 1751, and at the age of 12 was sent to England for his schooling. He received his medical degree at Edinburgh, and returned to practice in Charleston. He was one of the founders of the Medical Society of South Carolina and was for a long time the Parish doctor for St. Philip's Church. He died in 1793.

David Ramsay (1749-1815), famous as a pupil of Benjamin Rush, as Revolutionary patriot and statesman, historian and practitioner had something to say about children in a dissertation which he made to the Medical Society of South Carolina in 1790, "On the Means of Preserving Health in Charleston and the Adjacent Low Country." Said he: "The Object of the medical profession is not only to heal diseases, but to prevent them. The foundation of good health through life, should be laid in a proper treatment of infants. Their limbs should be unconfined, and frequently rubbed. Their food ought to be plain and simple. They should be constantly clean, and never suffered to remain wet for any length of time. Caps should be laid aside after the third or fourth month in winter, and much sooner in summer. Shoes and stockings may well be dispensed with through the whole period of infancy. Every prudent exertion should be early made for hardening the constitution against sudden changes of the atmosphere. To this end exercise should be freely and daily taken in the open air. When the weather turns suddenly cold, some additional clothing may be proper; but it is often more for the interest of children to habituate them to all the differences of our weather, and even to expose them to occasional colds, than by an excess of care and tenderness to induce a delicacy of habit. . . .

"In nursing cradles are hurtful. They add much to the heat of the infants who are confined between their narrow sides. A hard mattress is much cooler and on many accounts preferable. The youths who are accustomed to sleep on the floor with bare blankets will pass through life with more independence and with greater advantages than they who are accustomed to the relaxing indulgencies of soft beds. . . .

"In general it may nevertheless be safely affirmed that a great majority of our children would have a better chance of escaping the diseases of infancy, if they were from an early period of life habituated to the frequent use of the cold bath; and that very few cases occur in which the daily washing of them in cold water would not be of advantage. . . .

"Providence has kindly furnished us with an efficacious remedy for worms. Pink root is one of the best vermifuges in the world, and the seasonable administration of it to our children, would save them from what often proves a source of disease and death. . . .

"The months of April and May have been found by long experience to be unfriendly to children in Charleston. Parents should, therefore, make arrangements for keeping them out of the city during these two months. Country air is of singular utility not only for preventing but curing that vomiting and purging which attacks children on the approach of warm weather. Where a retreat to the country is not practicable, the next best preventative of this dangerous complaint is cold bathing. . . .

"The stomachs and intestines of infants should be well cleansed soon after they are born. That mothers should rest for several hours after their delivery is advisable. While they are recruited by repose after the sufferings of parturition, their offspring may be prepared for sucking with safety. This can only be done by thoroughly emptying their stomachs and intestines. . . .

"On this occasion give me leave to observe, that the writings of physicians who have

practised in colder climates are not applicable to this country. They represent the first milk of mothers as sufficient to carry off the meconium of new born infants, but the contrary is known to every practitioner of physic. Milk either has not the same qualities, or does not produce the same effects in warm as in cold countries. In this climate it not only often fails in carrying off from new born infants those crudities the retention of which gives rise to many diseases, but instead thereof, by mingling with them produces such disturbances in the alimentary canal, as frequently issue in immediate death. Much of the mortality among children especially on plantations, is owing to this cause. Overlaying, which is commonly said to be the occasion of their death, takes place much seldomer than has been supposed. The locked jaw of infants frequently arises from the irritation excited by the mixture of milk with meconium. If there is any one direction of primary consequence for preserving the health, and even the lives of infants, it is to empty their stomachs and bowels well before they are suffered to suck plentifully. A due attention to this matter would annually save many lives."

George Logan, the writer of the Edinburgh thesis, transmitted his interest in pediatrics to his son George,[12] who graduated at the University of Pennsylvania in 1802, and published in Charleston in 1825 "Practical Observations on Diseases of Children," a book adapted, as the author says, as well to the use of the practitioner as to the comprehension of country residents. Indeed some echoes of his father's thesis may be suspected. There is still the emphasis on breast feeding or wet nursing, or weak milk and gruel with sugar as a last resort. Pediatric ailments called for ipecac, salts, castor oil, magnesia, calomel, antimony, quinine, seneka snakeroot and blisters. Tetanus comes from improper care of the navel; nevi may be the result of prenatal impressions when they resembled fruit or animals. Clipping the tongue is seldom necessary. Cyanosis is due to an open foramen ovale. Ophthalmia can be treated with zinc sulfate. In an epidemic of this disease in the Charleston Orphan House (1824) the author practiced the "division of turgid vessels of the sclerotica." He advocated vaccination with cowpox at the age of 10 days. One observation of his has not been repeated until recent years, that "acute rheumatism, or a rheumatic state of fever, is not an unfrequent occurrence in this country, in children."

It would be foolish to claim that these Charlestonians made any serious contributions to medical knowledge, but they were interested, they wrote, and their names might not be forgotten in the record of early American pediatrics.

Acknowledgment

For the translation of the thesis of George Logan the elder, the writer is much indebted to Prof. Norman Chamberlain of the College of Charleston.

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SPANISH ABSTRACT

Bosquejo Histórico de la Pediatria en Carolina del Sur

Antes del siglo XIX relativamente pocos artículos de Pediatría fueron publicados en los Estados Unidos. En este bosquejo histórico se mencionan autores prominentes de Charleston que como Kilpatrick, Dale, Chalmers, Ramsay and Logan quizás constituyeron el nucleo inicial de interés pediatrico que estimulo a otros grupos del país.

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Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

THE report of the Committee on Medical Education will appear in full in the minutes of the Executive Board. Your earnest attention to this summary is desired. I shall refer to it only briefly here.

I wish to emphasize that here we have a committee with a problem and they have solved it well. The goal they sought was the continuation of the work begun by the Educators' Conferences under the sponsorship of the ICH Committee. Not only have they carried on these conferences, but they have enlarged and improved them.

As I have pointed out before, other committees have done equally well with their assignments, but the significance of the work of the Committee on Medical Education is that it was assigned one of the great projects of the ICH Committee. We have not let that committee down nor have we let ourselves down. The Committee on Medical Education has underscored the great object of our society "to establish and maintain the highest possible standard for pediatric education in medical schools and hospitals, pediatric practice and research."

This committee made two innovations. Prior to last year the United States and Canada were divided into 10 regions, so that there were 6 to 11 medical schools in each region. Last year it was divided into 8 regions and the Canadian schools met with the United States representatives. This year the Canadian medical school representatives met as Canadians and the conference was held in Toronto. This was done because they have problems individual to themselves and it turned out to be a wise move. They had a conference which they regarded as an epoch in Canadian pediatric teaching. Every Canadian medical school was presented.

The conferences, which were held at convenient times during the academic year, were well attended, especially by the educators themselves. One of the problems encountered previously and again this year was the small representation of state and district chairmen. These members, primarily practitioners, felt that this meeting would be a discussion of academic curricula only, in which they had no immediate interest. The discussion was not this circumscribed at all. The agenda in each case included some discussion of curricula, but for the most part the topic was "How pediatric education can best meet the

needs of the general practitioner, the pediatrician, the public health worker, and the local community." That, these conferences emphasized, is the true scope of pediatric education. When the state chairmen realize this, they will come.

This committee has gone further than its predecessors in that it is arranging a panel discussion on pediatric education at the annual meeting in Toronto. There the same type of theme is to be given to the membership. Speakers on this panel will be a dean of a medical school, a professor of pediatrics, a practitioner of pediatrics, a practitioner of pediatric surgery, and a pediatric psychiatrist, and a member of the Board of Pediatrics. Opportunity will then be given every member in attendance to state his objections or assents to the way pediatrics is taught today. There will also be an exhibit which will graphically describe pediatric education not only for the medical student, but for the graduate and postgraduate student and the practitioner.

I hope this letter will accomplish two results. First, I hope you will be induced to read the full report of this committee which will be sent to each member. The summary will be subsequently published in PEDIATRICS. Second, I hope that it will serve to demonstrate that this year the Academy has not only integrated into its structure those valuable projects initiated by the Committee for the Improvement of Child Health, but it has enlarged and extended them. This is what we set out to do and it has been accomplished, not only by this committee, which is used as an illustration, but by many other committees on whose work I have commented throughout the year.

PAUL W. BEAVEN, M.D., *President*

Round Table Discussion

LESS COMMONLY RECOGNIZED ALLERGIC CONDITIONS IN INFANTS AND CHILDREN

ARTHUR J. HORESH, M.D., Cleveland, *Chairman;* W. AMBROSE MCGEE, M.D., West Palm Beach, Fla.; M. G. PETERMAN, M.D., Milwaukee
W. EUGENE KEITER, M.D., Kinston, N.C., and JAMES G. KRAMER, M.D., Akron, Ohio, *Secretaries*

Chairman Horesh: For many years the Academy round table discussions have been on the commonly known allergic conditions in infants and children such as asthma, hay fever and eczema. These allergic diseases have now become familiar and are easily recognized by all pediatricians. In this round table discussion we will present conditions less commonly recognized as having an allergic etiology. It is now generally known that any organ or group of organs may be involved in an allergic reaction. The symptoms will depend upon the tissues sensitized, the degree of sensitization and the nature and amount of the allergen present. Investigations during the past decade have revealed an allergic basis for various well known clinical entities for which no clearcut etiologic background had been found. Every pediatrician is plagued by a host of complaints from parents about conditions which are extremely common, yet he can find little or nothing concerning their cause. Such conditions as poor appetite, disturbed sleep, habit spasms, nervous disorders, irritability, headache, stomach ache, frequent colds, poor resistance to infections, diarrhea, constipation, skin rashes, bed wetting and behaviour problems are only a few of the many problems which face the pediatrician with a private practice. Occasionally an organic basis is found for the symptoms but much too frequently "nothing is found." Thus for many of these problems the pediatrician has had very little to offer other than the old familiar phrase "he will outgrow it." It is our purpose to alert the physician to the possibilities of allergic etiology and to demonstrate that much can be done for many of these childhood problems if the essential fundamentals of allergic knowledge are kept in mind.

Before commencing the discussion of these pediatric allergic conditions, I wish to review the criteria for the diagnosis of an allergic disease. In this discussion we will use the term allergy in the restricted sense referring to conditions known as atopic diseases. This form of allergy includes the common allergic syndromes such as asthma, hay fever and eczema and other conditions characterized by reversible tissue changes which are activated by antigens producing wheal-like reactions, increased capillary permeability, edema, smooth muscle stimulation and increased activity of mucous glands.

A symptom or group of symptoms may be considered as allergic (atopic) if:

1. They are not adequately explained by other means.
2. There is absence of clinical findings of an organic nature.
3. There is a strong family history of allergy.
4. There is an associated allergic condition in past or present history of the patient.
5. They are ushered in with manifestations which are unquestionably allergic, i.e., a gastrointestinal disturbance preceded or accompanied by hives or a headache preceded or accompanied by frequent sneezing and rhinorrhea.
6. They are associated with eosinophilia of blood and mucus secretions.
7. They recur seasonally.
8. They recur in periodic attacks.
9. They are of a chronic nature.
10. They are of a benign nature.
11. They are relieved by the administration of epinephrine.
12. They are associated with positive skin tests.

From the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 16, 1950.

13. They are accompanied by the secretion of excessive amounts of mucus.
14. They are accompanied by intense pruritus.

All these characteristics are not found in every allergic disease. Also every one of its manifestations may be encountered in a nonallergic illness. In general it may be said that the allergic disease has no pathognomonic symptomatology. Its recognition, therefore, depends upon the suggestive coincidence of many of its characteristics.

We will discuss the pediatric allergic conditions by systems. Gastrointestinal manifestations of allergic disease will be considered first. Some of these are: cheilitis, glossitis, canker sores, gingivitis, geographic tongue, parotitis (recurrent), nausea (chronic), vomiting (recurrent), abdominal pain, gaseous distention, cardiospasm, pylorospasm, colic, gastric symptoms simulating peptic ulcer, constipation, diarrhea, mucous colitis, celiac syndrome, clay-colored stools, biliary colic, intestinal bleeding, ulcerative colitis, excoriation of buttocks, pruritus ani, anorexia and malnutrition. The physician must always bear in mind that sensitization is only one of the many possible causes for the manifestations listed above and therefore a complete differential diagnostic study is imperative. Dr. McGee will begin the discussion on gastrointestinal manifestations.

Infantile Colic

Dr. McGee: The first symptom presenting itself in infancy which suggests allergy is so-called "colic." It seems that it is much more prevalent than it was formerly. This viewpoint may be due to the fact physicians are more cognizant of the existence of colic and are more willing to accept allergy as a factor. The stress and strain of our lives and the unsettled world affairs perhaps reflect themselves in the infant's make-up. The commercial propaganda that evaporated milk will agree with every infant plus the far too early introduction of multiple foods might be a factor.

When we are given such an unhappy baby as a colicky infant, what should we do to overcome or alleviate that troublesome complaint?

At first let us be sure the infant is getting the optimum number of calories in the proper proportion, that the mechanism of nursing is correct, that a calm atmosphere prevails, that hunger is satisfied, etc.

If the infant is on powdered, evaporated or boiled milk, try a modified cow's milk formula, as Similac®, or a low fat one, as Dryco®. With no improvement in symptoms after a minimum of 4 days, use a different animal's milk, such as goat's milk evaporated, boiled or powdered formulas, as the lactalbumin in all animals' milk varies.

From animal milk we turn to "vegetable" milk as Mull-Soy® or Sobee®. The lactalbumin and casein of milk are different from the protein of vegetable milks. Many colicky and other types of allergic infants do well on those milks and in a few months the majority have developed sufficient tolerance to milk to return gradually or even suddenly to it.

For the minority of infants who still are miserable an amino acid milk such as nutramigen® is helpful. It is unfortunate that completely hydrolysed proteins taste so terrible but, fortunately, infants in the first few months of life will usually accept such a formula.

Where failure still prevails, results may be obtained by strained meats to which, of course, must be added fats as soy bean oil, carbohydrates, minerals and water. It is surprising how well such meat formulas are liked and tolerated, even by little infants.

In a few cases none of the preceding suggestions meet with success. Here all we can do is alternate, as soon as trouble begins, between 2 or 3 of the formulas which give fewer or less severe symptoms.

Of course, antispasmodics, antihistamines and sedatives are indicated and should be attempted, so long as needed.

Fortunately, nature comes to the rescue of the colicky infant and the floundering and puzzled parents and pediatrician, and at the age of 3 to 18 months, nearer perhaps 6 to 12 months of age, a tolerance to milk is built. But, do not be misled and say, "Thank God, this is over," for at the age of 2½ to 5 years, when children often gather together, trouble begins in a different form. The previously colicky infants now develop recurrent or chronic head colds, croup, bronchitis, so-called sinus infection and/or headaches, stomach aches, nausea, vomiting, diarrhea. They usually are irritable children who have a short span of attention.

Colicky infants are generally poor vegetable eaters and usually have finicky appetites.

To reduce subsequent allergic reactions in colicky babies, introduce very slowly vitamins and

foods and then preferable synthetic vitamins and single foods. Allowing an interval of first 5 days, then 3 days, when introducing a new food or vitamin often keeps untoward symptoms at a minimum and gives a means of detecting offending foods and vitamins.

Where both parents have allergic backgrounds, practically all children will become allergic in some manner, the allergy manifesting itself sooner when their parents' allergy is clinically active. With a unilateral history of allergy, half their children become allergic victims.

Other gastrointestinal symptoms suggestive of allergy in young children are excessive regurgitation, constipation, recurrent diarrhea, mucus in the stools, perianal erythema, gaseous distention, pyloric spasms.

Dr. Maurice Kaufman, Lexington, Ky.: How long would you say a child should be off a food before you would say that particular food had nothing to do with the allergy?

Dr. McGee: I think it depends on the symptoms; pain may clear up in a few days but eczema might take a month to clear up.

Dr. Harry Lowenburg, Jr., Philadelphia: How frequently do you find eosinophiles present in the stool in intestinal allergy?

Dr. McGee: I have often said that it is frequently absent so I haven't been very lucky in finding eosinophiles in the stool in gastrointestinal allergy.

Dr. P. E. Williams, Hamilton, Ont.: With a colicky baby do you really get good results when you take them off cow's milk and put them on goat's milk? I haven't had much luck with it.

Dr. McGee: Cow's milk and goat's milk have a common antigen—the casein factor. In casein sensitivity there will be no improvement with goat's milk.

Respiratory Tract Manifestations of Allergic Disease

Chairman Horesh: The common respiratory tract manifestations of allergic disease are: asthma, hay fever, perennial allergic rhinitis, wheezing, cough, tracheitis, bronchitis, bronchiectasis, angioneurotic edema of the larynx, croup, pharyngitis, tonsillitis, sinusitis, enlarged tonsils and adenoids, epistaxis and frequent colds. When some of these symptoms occur alone as the sole manifestation of the allergic state, they frequently go unrecognized as allergic symptoms. Dr. McGee will discuss some of the respiratory manifestations.

Respiratory Manifestations

Dr. McGee: Allergy of the respiratory tract presents bizarre symptoms and signs. It may affect any part of the tract in various ways.

The early symptoms in infancy are recurrent or chronic nasal discharges and blockage, excessive sneezing, coughing, hoarseness and wheezing. These recurrent symptoms are often labeled as infectious in origin. However, an absence of any appreciable fever or loss of weight or appreciable evidence of acute illness does not favor such an opinion. The individual so affected may have other types of allergy and often a family history of allergic disorders can be found on close inquiry. In spite of chronic symptoms those children do not usually appear below par for their chronologic age and family type of inherited stature. As a group, they stand sudden weather change poorly and often do better with windows closed at night.

On physical examination a few signs stand out. They are often nose-rubbers or snifflers and often have a barking cough or clear their throats frequently. Those with such nasal blockage often become mouth-breathers like adenoid patients. In the latter there are often associated ear infections, malnutrition, adenoid expression and failure of appreciable relief from antihistamines. The inferior turbinates may appear grayish or whitish in color with or without edema. Smears from the turbinates or nasal secretion often show an increase in eosinophiles. There may be puffiness in the area beneath the outer third of the lower eyelids and subocular discoloration. These children are over-active and have a short span of attention.

Treatment directed locally, as has been so prevalent in adults, is without results. Nasal drops are seldom used, since the use and abuse of antihistamine drugs. Allergic surveys adequately made and followed by dietary control with or without antigen injections produce good results where cooperation is obtained.

Those infants who were colicky for several weeks or longer will often be victims of so-called "head colds" for a few days or weeks before the eruption of each single or group of deciduous teeth. Such an idea might appear unscientific to some pediatricians but not to those who have allergic

children of their own. When confronted with such a problem it is wise to defer the introduction of new foods or vitamins for a "head cold" might be the type of adverse reaction experienced from that new food. Apparently these "teething head colds" are associated with a latent allergy which becomes manifest only when an infant is under stress or strain. Here, perhaps, pain or discomfort from the tooth erupting gives rise to some inbalance between the sympathetic and the parasympathetic systems. The infant's gun is loaded, so to speak, whereas the discomfort of teething acts as the trigger.

The minority of so-called sinus infections of childhood are hardly more than the result of nasal allergy. The infection is secondary to blockage of sinus openings due to edema of turbinates. Local treatment, x-ray irradiations, nasal drops and antihistamines in such cases are not of lasting value as no attempt is directed to removing the cause. Here we are only treating the result. Adequate allergic survey and treatment based upon such a study is productive of good result in the majority of cases.

The removal of tonsils and adenoids for repeated allergic head colds or sinusitis per se usually results in complete failure. Where there is a history of repeated acute attacks of tonsilitis or adenoiditis or evidence of infected tonsils and adenoids, a tonsillectomy and adenoidectomy is definitely indicated and may help an accompanying nasal allergy. It is far better to remove infected tonsils and adenoids in the season when pollens are absent or less prevalent. Such a precaution reduces the subsequent danger of pollen hay fever or asthma which far too frequently develops in a year or so.

Dr. Robert J. Mason, Birmingham, Mich.: On giving the skin tests do you recommend that the average practicing pediatrician who is not particularly qualified or trained in allergy do intradermal skin tests?

Dr. McGee: It is perfectly all right to use scratch tests if you use them adequately but not intradermal unless you are trained in it and have plenty of time to spend in the phase.

Chairman Horesh: We have adopted a rule that we never do an intradermal test until the scratch test for that particular substance is negative.

Central Nervous System Allergy

Chairman Horesh: In recent years the interest in nervous system allergy has increased among allergists, neurologists and psychiatrists. However, the possibility of allergy being a factor in many common nervous system manifestations is not yet generally recognized nor fully accepted. Clinical conditions such as migraine headaches, cyclic vomiting, epilepsy, narcolepsy, Ménière's disease, peripheral neuritis and mental disturbances have been studied from an allergic standpoint and have been claimed, at least in some instances, to be allergic in nature. We are fortunate to have Dr. M. G. Peterman with us today to discuss the subject of epilepsy.

Dr. M. G. Peterman, Milwaukee: There is no longer any doubt that epilepsy is an inherited disease. The fact has been established by the electroencephalogram but the peculiar nature which has not been established is why most children go 8 or 10 years before having the first seizure. Then the sequence is established and seizures continue to recur. What precipitates the convulsion, what is the inciting mechanism is not known. There are multiple factors which might be responsible. There are multiple factors which might affect the personality and the behavior of the child. It has also been pretty well established, what every general practitioner knows, that many seizures in the child with epilepsy are associated with some food disturbance. Either he has ingested an enormous amount of food, such as nuts or popcorn, or he vomits food which he has taken 2 or 3 days before, or he has a history of constipation. The gastrointestinal factor has never been explained but without a doubt it is a common one and has to do with the trigger mechanism. It has to do with the preparation of the organism which causes this discharge which we may register on the electrogram, but which we cannot otherwise explain. There is no reason that allergy could not be a factor or one of the factors in the trigger mechanism which precipitates the explosion or the convulsion or the electric discharge which we know as the convulsion. Also, we have never been able to explain the factor in the ketogenic diet which has made it the most effective treatment of epilepsy known.

When we started the ketogenic diet, we went on the basis that fasting was the most effective treatment known for epilepsy. There is no doubt of its effectiveness, there is no doubt of its value; anyone may establish that. We set out to produce a diet which had the chemical effect of fasting and still allowed enough calories to provide for physical activity and maintenance. Wilder approached

it from a chemical point of view and at that time I must say that I was not only skeptical of allergy but, knowing little about it, had the typical medical reaction. I am glad to say that I have changed my point of view and realize the possibilities of allergy. I think that there is no doubt that the restrictions which the ketogenic diet demands eliminate a number of foods or combinations which might be a factor in precipitating convulsions.

Dr. John J. Slavens, Toronto: May I ask Dr. Peterman about the inclusion of water or restrictions of water in the fasting?

Dr. M. G. Peterman, Milwaukee: Water restriction has been carried as far as was physically possible. We have studied water metabolism and do not think it is a factor. The immediate change is a spasm of the blood vessels in several areas. That change might be something similar to an asthmatic attack. It is a vascular disturbance. But we do not think it has anything to do with water. We have tried water restriction which we know is difficult in a child. One can restrict only so far and then the temperature goes up and water must be given. The younger the child, the more important the water and the greater amount necessary. The older the child, the more drastic the water restrictions can be and yet that does not seem to be the factor in epilepsy. I thought once it might have an important advantage in reducing or preventing cerebral edema of the brain. Now I know that drastic fluid restriction is not reflected in the brain. In allergy conditions one may reduce the water so much but the vascular spasm will occur just the same. The present theories on water metabolism must be thrown out. It is more likely the chemical change such as the sodium content of the brain which directly influences water metabolism which in turn influences vascular spasm of the brain.

Chairman Horesh: Thank you all. Our time is up. I am going to close this Round Table with the following brief summary:

1. In allergic reactions, almost every organ or part of an organ may be affected, the symptoms depending upon the tissues sensitized and the degree of sensitization. Allergy may simulate practically every organic disease. If no organic cause for the symptoms under consideration has been found and before either the child or his parents are branded as neuropaths or psychopaths, allergy should be considered. The current fashionable swing of the medical pendulum to psychosomatic medicine has unfortunately resulted in labeling any disorder for which no immediately obvious inflammatory, neoplastic, metabolic or traumatic cause can be found as psychosomatic. Unless specifically looked for, the diagnosis of allergy will be missed.

2. We wish to stress that the presence or absence of skin test reactions is not the one deciding factor in establishing a diagnosis of allergy. Cutaneous tests for sensitivity have attained a deservedly important place in the specific diagnosis of the cause of allergic diseases. However, like all the tests they deserve serious consideration only when properly done and the results well evaluated.

3. The child with low resistance to infection is a major pediatric problem. As pediatricians we must be more alert to considering more carefully the host and the factors influencing susceptibility. Lawrence Henderson and W. F. Petersen have repeatedly emphasized these other factors, including the organic state of the patient. To believe that bacteria plus human equals disease is an oversimplification of ideas. We must recognize that it is bacteria plus the kind of human, plus the state of the human that equals disease. An allergic disturbance can so change the state of the organism that the sensitized tissues—be they in the nose, throat, tonsils, ear drums, larynx or bronchial tubes—become the seat of inflammation from bacterial invasion. Otherwise quiescent bacteria become active as a result of the allergic reaction. Other impacts may do the same such as heat, cold, physical or emotional trauma. But in infants and children the allergic constitution is a major factor in low resistance to disease.

4. On the other hand, we wish to warn against over-enthusiasm and blaming allergy for all unsolved problems in pediatric practice. There may be a tendency in handling pediatric patients to forget that we usually have many different causes for the symptoms in question. We must not make the mistake of treating obvious pediatric problems along allergic lines, forgetting well founded old methods of treatment.

Round Table Discussion

CHILDHOOD ACCIDENTS AND THEIR PREVENTION

HARRY F. DIETRICH, M.D., Los Angeles, *Chairman;* GEORGE M. WHEATLEY, M.D., New York City; GLIDDEN L. BROOKS, M.D., Pittsburgh
ROBERT H. KOTTE, M.D., Cincinnati, and DOROTHY WYVELL, M.D., Midland, Texas, *Secretaries*

Chairman Dietrich: We wish to direct attention to the much neglected problem of accidents in children. It is a unique one. The ultimate solution rests on child-parent relationship, and we as pediatricians are responsible for guiding that relationship. So far, the medical profession's attack on the problem has been piecemeal, perfunctory and without potency. For this round table discussion, our plan is as follows: Dr. George Wheatley of the Metropolitan Life Insurance Company will present the size and shape of the accident problem, Dr. Glidden Brooks will indicate the hospital's role in the problem of accidents and outline the research needs in this field, I will briefly outline what I think is a practical theory of accident prevention, and Dr. Wheatley will sketch some areas of thought on community organization for accident prevention.

Dr. Wheatley: Pediatricians are well aware of the child accident problem. But they are apt to look at it almost exclusively from the point of view of the day-to-day treatment of pediatric emergencies. Unquestionably proper management of accidents is important but it overlooks the basic approach in solving the problem. This major concern with accident-treatment contrasts with the modern pediatrician's orientation toward disease prevention.

What are the facts? The highest accident fatality rate is found in the preschool age group from 1 to 4 years, the period during which most of the children spend more of their time in the home environment under closer supervision than any other period in their lives. The remarkable conquest of the common childhood diseases has sharpened our focus on the child accident picture. In preschool age children the drop in mortality rate for all diseases combined for the period of 1930-1947 has been almost 70%. Over the same period and in the same age group, the accident death rate declined only 23%. The accidents which occur more frequently in the 1 to 4 year age group are fatalities caused by motor vehicles, closely followed by those resulting from burns and conflagrations. These causes combined account for more than 60% of all fatal accidents in this age group.

About one fourth of all fatal accidental poisonings are in children of preschool age. Most of these are concentrated in ages of 1 and 2 years. This is, as we know, a particularly inquisitive period. In most cases, the fact that such young children were able to get at known poisons indicates some adult's carelessness, not only in handling the poisons, but also in supervising the child. Many other cases indicate that parents simply do not realize the number of substances in an ordinary home which can poison a small child if he manages to get hold of them. Some of these fatalities would probably have been avoided by more careful supervision. A knowledge of first aid might have saved others. For similar reasons, fatalities due to choking are by no means rare. As with accidental poisoning, the age when these deaths occur is significant. About 9 out of every 10 deaths due to ingestion of poisons or choking on a foreign body are in children aged 1 and 2 years.

Chairman Dietrich: I think it is worth emphasizing that while the death rate in children from all causes has dropped over 90% in the past 50 years, the rate from accidental death has been too nearly constant. At the present time, and for all age groups after 1 year, accidents are the most common cause of death. Over 12,000 children are "accidently" killed in the United States each year.

Dr, Brooks: The topic assigned for me to discuss is "The Importance of the Problem from the Standpoint of Hospitals and Communities—Research Needs."

As in any research activity, the basic and primary need is, of course, as accurate and complete a measurement of the problem as is possible. Such a measurement then makes possible the intelligent

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delineation of areas both for further study or for direct action. Dr. Wheatley has just presented data of the type to which I have reference and has spoken of the need for more statistics, especially from the standpoint of morbidity. I believe that it is necessary for each community to develop a system of collection of data so that it may study its individual problem of accident prevention more effectively. Assuming that one is developing a system for collection of statistics having to do with childhood accidents in a community, some of the data one would obviously want are the number of accidents, the seriousness of the type of accident, its location, the age of the child involved, and something about his general social and economic background.

Other factors which might appear in our data have to do with the economic situation. We must have the answers to: How many children are hospitalized as the result of accidents? How long do they remain in the hospital? Who pays the hospital bill? How much time from work is lost by an income-producing parent?

Since most significant accidents to children come to the direct attention of the community hospital, this might be a logical place to centralize collection of such data. The hospital, after all, is the place where the doctor, the parent, the child, the police force and other groups in the community dealing with the problem of accidents meet most often.

A second general category of research for which there is need is the study of the individual child. It is in this area that we, as pediatricians, have a special obligation. For example, here is a little boy, 10 years old, named Stanley, who came to the Children's Hospital of Pittsburgh in August of this year. In the previous years he had been seen for 10 different accidental injuries. There are many such children and each requires careful, individual study before a label such as "accident-prone" can be applied. It is obvious that this boy is adventurous, but is he accident-prone, or just unlucky?

The third general area in which research is needed lies in the development of preventive measures. If we have accumulated and analyzed data about the mass of children, so far as accidents are concerned, and have arrived at a few generalizations as the result of the study of a number of individual children, we are then in a position to develop a whole series of preventive measures or programs whose emphasis and limitations are based on this data. We must, however, not be content with simply establishing a program based upon sound data but we must constantly evaluate and re-define these programs.

The fourth and final general area for research lies in the field of continued development of therapeutic measurements. These measures are designed to minimize the effect of those accidents which, in spite of our best efforts, we fail to prevent.

Finally, having developed data and programs in individual communities, some thought must be given to making such data more than locally useful. Therefore, it might be advisable to constitute some form of state or nation-wide cooperation so that a uniform system of recording, classification and interpretation of data can be developed. One might visualize, for example, a joint committee representing those national organizations which impinge upon this general field of accident prevention to children. All these activities which we have just discussed depend for their consummation upon an awakened interest in one of the most serious problems in child health today; a problem which is not only medical in its scope but requires the participation of many persons in many fields of endeavor.

Chairman Dietrich: I have been emboldened to suggest that it is possible to formulate a practical theory of accident prevention. The multiplicity of variables in childhood has apparently discouraged such an attempt, but if one deals with the means of prevention rather than the individual situations, such a formulation does not seem impossible. The two factors needed for the prevention of accidents at any age are protection and education. During the first year of life, when the child is not skillful at dodging, he must be given exactly 100% protection against burning, drowning, poisoning, crushing and mangling. At 5 years of age, both school and play remove the child from the protective devices established by the parents, and principle reliance must be placed on what the child has learned. Obviously, the years from 1 to 5, must be occupied by increasing educational experience and decreasing protection. While the parents maintain protection against the lethal and crippling hazards, they must be imaginatively and progressively teaching the youngster the ordinary hazards of living. If we plotted the roles of protection and education in a horizontal rectangular frame representing the first 5 years of life, a reciprocal relationship between protection and education would emerge. This is the theory of accident prevention in children. Its practical application in the home requires forethought (stimulated by pediatric counsel), time (borrowed from the time we allow parents to

waste on needless and useless worries about their children) and discipline (which is so essential to a child's sense of security). Safe behavior is a primary facet of normal behavior. It seems reasonable to give parents accident prevention advice at the same time that they are given other immunizing procedures. Now, Dr. Wheatley, what about community organization for accident prevention?

Dr. Wheatley: First, there should be a sponsoring agency. It could be a committee of the local medical society or it might be a health department with a health officer who understands the problem and has a plan to reduce the child accidents. Some communities have safety councils which have so far been partially interested in industrial safety problems and sometimes this interest reaches the schools, but they have had no access to the age group where we see a large part of this problem. They might conceivably be the sponsoring agency but they do need the help of the other agencies in the community. The sponsoring agency should call a meeting of other interested organizations. At a meeting, the sponsoring agency should outline the possible activities that the community groups might carry out. Representatives from the health department, parent teacher association, tuberculosis association, etc., would be expected to tell what they could do to help. One important result of such a meeting would be to form a child safety committee to carry on the activities outlined at a meeting. For example, what could a medical society do? Suppose you are representing your medical society. One of the unique contributions of the physician is through his hospital. What kind of accident facts can be obtained through the hospital? How should the records be kept? Has your hospital considered accident prevention as an ideal medium public relations project?

Another way to bring accident prevention program to the fore in the hospital is through conferences to discuss accident cases. These meetings would be comparable to the pathologic conferences or history meetings. Not only the treatment, but the preventive, economic and social aspects of the cases should be discussed.

Chairman Dietrich: Before inviting comment and questions from our group I must warn you that at first you are going to find that parents are cool and physicians are casual about the accident problem.

Dr. Joseph S. Wall, Washington, D.C.: I was asked to speak on a television program during this meeting and prepared something on the hazards in modern child life. We had a program depicting accidents by automobile and by poison, and in answer to Dr. Wheatley's question, we had about 260 poison cases at the Children's Hospital in Washington in a 4 year period, 2 of which were fatal. I believe that we can do a great deal in the way of education of the child, his parents and his physicians. Physicians are the ones who come in contact with the results of accidents; they ought to know something about accidents. They ought to know what produces accidents, through research, and then put in practice what we have learned. Once a year we put on an accident conference during our Sunday morning conferences in the hospital. I see no reason why the pediatric group in any county medical society couldn't put on something with all the membership in relation to this point. Then I think we could reach others through the lay organizations that were mentioned here, and then through television, such as we had this morning.

We must impress the public but we must not make it too boring. Here is a pair of pants that look as if they have leopard spots, because they were on a child when he drank clorox. Now I think if we could show the mothers some of these things it would make an impression on them and teach them something. I do think that we want research. The organization conducting research in our town is the Red Cross and if we could determine through research what are the environmental factors causing accidents and what is the trigger mechanism that sets them off we might be well repaid.

Dr. Herman Marks, Providence, R.I.: I agree essentially with everything that has been said except I wish, Dr. Dietrich, you hadn't been in such a hurry to use the eraser on "mental health" because I think there is a very definite relationship between childhood accidents and what we may loosely designate as "mental health."

We have been shown a graph to illustrate the relative importance of protection and education in the prevention of accidents at various age levels. I submit that the degree of protection and education against accidental hazards that parents give to children and the extent of protection and education children accept from parents are determined by the nature of the parent-child relationship. All accidents are not really "accidents," as studies of accident-prone adults and children will show.

Dr. Wheatley tells us that the accident rate in children climbed during the war years as mothers left homes to enter defense factories. It would be interesting to know, and I doubt whether we could

even ascertain with certainty, how many mothers were motivated to leave their homes by patriotism, for financial gain, for change of scenery, or for unconscious rejection of their children.

We may lay down rules to minimize accidental hazards and to reduce their incidence and this is all to the good and commendable. But it is well to remember that we are just beginning to learn about the children who, without being aware of it, seek injury to gratify certain complex instinctual needs and parents who in equally neurotic ways somehow can neither afford their children nor wish to give them the education to prevent sometimes frequent and sometimes tragic accidents. As pediatricians, we are in a particularly strategic position to observe and sometimes modify some of these unhealthy parent-child relationships that may contribute to "accidents" in childhood.

Dr. Victor C. Vaughn, III, New Haven, Conn.: May I amplify an idea which is tangent to Dr. Mark's remarks—that is, the type of discipline which we indulge in has to be oriented toward the particular kind of accident prevention in which we are interested. I have in mind the experience in our neighborhood of two 2 year old girls who have a tendency to enter the street. The practice of one of the mothers is to pick up the child and put her right back on the curbstone and give her the rest of the block to play in; whereas the other mother takes her child in the house and doesn't let her come beyond the door. Thus a limit is put on the child's activity which may seem unreasonable in terms of specific safety precautions. I think it would be lots of help to our parents if we tell them how to discipline. You don't necessarily keep the child out of the kitchen because he is likely to burn himself!

Chairman Dietrich: Doctor, we could have a real good argument on the latter point if we had time.

Dr. Donald D. Posson, Rochester, N.Y.: I don't think you need to be afraid of a community program because of the cost. In Rochester we put on just such a program about a year ago and found enthusiastic response from all the different departments, police, PTA, Red Cross, and everyone up and down the line. We put on a child safety workshop which lasted all day. This was well attended and we felt that we could carry the program right into the home through the PTA, visiting nurses and other groups.

I think that physicians themselves don't do the missionary work that they should do in preventing child accidents. Most of us practicing pediatricians go into the homes in making home calls. There is hardly a family whose home set-up we don't see. Every day I see accident hazards. A bowl of peanuts set on a coffee table where the toddler can get hold of it, unguarded stairways, boiling liquids on the stove, poisonous cleansers and insecticides—all these should be pointed out as potential sources of accidents. We have a unique opportunity as physicians to instruct in safety, and the parents will take it better from us than they will from the PTA group or anyone else. We have had several deaths from oil of wintergreen; a kind neighbor suggested that a woman give her daughter a teaspoonful of oil of wintergreen to stop her colic—she stopped the colic and killed the child.

We have recently had a death in our city from boric acid dusted into the diapers of the child to stop diaper rash; this child absorbed a toxic amount. I think we ought to work toward eliminating boric acid as a household substance because it is much more dangerous than realized.

Dr. Harriet W. Nielsen, China Lake, Calif.: I wonder if a list of such poisonous things as boric acid and bromates might be included in one of our journals. It might be a long time before they would appear as case histories and it might be easier to refer to a list in a journal to see if anyone else has had similar experience.

Dr. Posson: The University of Rochester Medical School Pharmacology Department is working on a pamphlet of poisons which will list these poisons by their brand names, and will try to have this available for practicing physicians and drugstores in 1951.

Dr. Robert Warner, Buffalo, N.Y.: I want to know how we as pediatricians can stand up and be the leaders in this thing when pharmaceutical houses are putting out candy aspirins, and we know that the aspirin bottle is one of the chief causes of poisoning. We of the Academy here accept, support and sponsor these houses who put out the candy aspirin; we give out the candy aspirin. You can't teach a child the difference between one kind of candy and another and it seems to me that is and should be our duty to prevent the manufacturer of these "candy" medications.

Dr. Donald Court, Newcastle-on-Tyne, England: Is the hospital alone equal to the task of measuring the total morbidity from accidents in the community?

Chairman Dietrich: No, I don't believe it is, particularly in a larger community, but it can be the

nidus from which such studies radiate. In Los Angeles, we started at the Children's Hospital, then Miss Buckwell of the Public Health Department began studies, and we are now planning surveys of home accidents in industrial families.

Dr. Court: What part can the law play in accident prevention?

Chairman Dietrich: We need only call attention to the traffic situation to answer that. You can prevent some accidents by law, but for the most part it takes a great deal more than that. When we speak of safety in industry or traffic we always refer to the 3 E's—education, engineering and enforcement. You can legislate on certain types of engineering, you can say that there have to be certain fire protective devices in a building, exits, etc., but you can't keep the tenants in that building from dropping matches in wastebaskets. Laws can help, I think, but slightly.

Dr. Court: Are accidents of little importance in the first year?

Chairman Dietrich: Statistically they are less important than in the later years because of the preponderance of neonatal deaths, which heavily weight the figures for the first year.

Dr. Harry Horwitz, Oakland, Calif.: Will you discuss office accidents caused by the detachable ear piece on the otoscope?

Chairman Dietrich: I am sure Dr. Horwitz has something specific in mind. The only accidents I have witnessed are the breaking of the detachable ear piece by the children.

Dr. Margaret Limper, Louisville, Ky.: Do you think that the current psychiatric thought that fear is poisonous to the personality has anything to do with the increasing proneness to accidents?

Chairman Dietrich: I know that I cannot give any opinion on that in a minute or 2 that would be worth that much of your time.

Round Table Discussion

THE PREMATURE INFANT

HEYWORTH N. SANFORD, M.D., Chicago, *Chairman*
J. HAROLD ROOT, M.D., Waterbury, Conn., and R. H. GRAHAM, M.D.,
Aurora, Ill., *Secretaries*

Chairman Sanford: Dr. Herman N. Bundesen, Commissioner of Health of Chicago, organized 12 years ago the "Chicago Premature Plan." This consists in registering all premature infants with the City Health Department within a few hours after birth. The premature infant who is born at home, or in a hospital that does not have adequate premature care, is transported in an oxygenated incubator ambulance to a hospital which specializes in such care.

From 1936 to 1947 premature infant deaths in Chicago have been lowered 6½%. The full term infant death rate during the same period has been lowered about 3%. Inasmuch as the premature death rate has been lowered about double that of the full term infant rate, we believe this procedure has been the cause of reduction. In 1936 there were 47,000 live births in Chicago. In 1947 there were 82,000, or an increase of 80%. In this number the full term infants increased from 45% to 60%, whereas the premature infants increased from 2000 to over 5000, or about 140% increase of premature infants born in Chicago during the last 10 years.

This adds a considerable increase to the number of infants for our available premature infants beds. Where formerly we planned 5 premature births to each 100 full term births, we now find that prematures have increased to 8 per 100 full term infants.

Causes of prematurity are multiple births, toxemia, heart disease, syphilis, tuberculosis, infections, accidents, premature separation of the placenta and abnormalities of the reproduction tract. It is generally understood that there is a tendency for more premature births among the Negro race than the white race. Our Negro population in Chicago has increased in the last 10 years but our increase in premature infants has not been racial. I have no explanation. Premature births certainly are increasing in this area.

I have been impressed with another phase and that is many premature infants that we see are from a cesarian birth. Obstetrics has produced more live births but at a premature level. We also find that abnormal pregnancies account for a much higher premature mortality less noticed in the lower weight group.

Any good feeding in the hands of a competent pediatrician is entirely satisfactory. In Presbyterian Hospital, Chicago, we use breast milk entirely as a food for our premature infants. This is obtained from our maternity mothers. We encourage breast feeding and most of our mothers have an excess which we pump and bank. The breast milk is frozen in 4 oz. bottles and stored in a deep freeze. This can be used as long as a year later with safety. The City Health Department operates a very efficient breast milk station and will furnish breast milk gratis to any premature infant born in Chicago. If we happen to have an excess, we give it to the City Health Department and they give us credit for it, and then if we run short, we borrow from them. In this way every premature infant is sure of obtaining breast milk. It is not necessary to use pure breast milk for all premature infants. You can use any good type of artificial food and dilute the breast milk with it up to about equal parts, and obtain almost as good results as with pure breast milk, except in very small infants or those who are sick. When we have such a baby, it is taken off our standard formula of equal parts breast milk and lactic acid and given pure breast milk. This formula is a great saving of pure breast milk.

How often should a premature infant be fed and how soon should they be fed? I think the usual tendency is to wait at least 24 to 48 hours, or even longer. They should be fed in the way that is easiest for the baby and easiest for the personnel. We gavage them at 4 hour intervals until the weight is about 4 pounds, then the nurse begins bottle feedings. In some institutions the premature infants

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are discharged at 4½ pounds. We like to keep them until at least 5½ pounds because we find that we gain bed space in the long run since fewer return with gastrointestinal upsets.

Dr. Charles E. Snelling, Toronto: I would be interested to know how many men in this group are using breast feeding for prematures?

Chairman Sanford: There are about 6 in this group of 33.

Dr. Hearn Bradley, Nashville: I would like to know how many men are using skimmed boiled milk with 10% added sugar.

Chairman Sanford: One or 2 of this group seem to be using this formula.

Dr. Harold J. Freedman, Boston: I worked in Chicago with Dr. Hess and was quite impressed with the method of using breast feeding, but when I went to Boston they weren't very much concerned with this system, perhaps because they did not have the set-up. We used 2% skimmed milk with highly concentrated carbohydrates. We generally fed them after 48 hours, starting with very small amounts and increasing very slowly. I wonder if you do the same thing?

Chairman Sanford: We allow the nurse to decide the increase as she can observe the baby's capacity better than anyone else.

As to accessory fluid, a great many will give dextrose or saline between feedings. In studies we made over a 10 year period, we found that 5% carbohydrate suppressed the amount of feeding that these children would take by suppressing hunger. We give only water by dropper between feedings, as much as the baby will take, and do not have to use intravenous or subcutaneous injection.

Lund and Kimbel in 1943 found that the premature infant received very little vitamin A from the mother and very little reserve was stored in the liver. The premature infant might, therefore, be deficient in vitamin A. Warkany found that rats deficient in vitamin A produced offsprings with eye defects. Clifford found that there was much better absorption of water soluble A to reach an optimum blood level of 29 units. We should, therefore, give about 20,000 units of vitamin A in a water soluble form.

Vitamin B, I believe, is unnecessary. Vitamin C is necessary for oxidation of amino acids, as well as against scurvy. There has been a tendency to increase vitamin C intake over the years and we find 150 to 200 mg. frequently given. Actually 50 mg. is usually sufficient and 100 mg. maximum. It makes no difference how it is given. It can be orange juice or combined as a multivitamin. Vitamin D is usually given in 1000 unit amounts.

It has been thought for many years that the premature infant had a lower prothrombin content of the blood than the full term infant. Actually this idea is based on a few studies of a small number of premature infants. We thought we would correlate the prothrombin estimations that we had made on the full term infants with similar studies on 100 premature infants. These studies showed that there is a decrease in prothrombin content of the blood in the premature baby during the first 3 days of life which corresponds to the decrease observed in the full term baby except that it is not as great and it rises faster. Like the full term baby, the prothrombin content of the blood can be increased by the administration of vitamin K.

In this study there were 83 premature infants who were given no vitamin K at all and 17 who were given vitamin K. While the administration of vitamin K increased the prothrombin content of the blood, it had no effect on the hemorrhagic manifestations. Those premature infants not given vitamin K had 6% of hemorrhagic manifestations, and those given vitamin K had 24%. However, this increase was due to the fact that this group was brought in from outside the hospital and had considerably more manipulation. These figures simply demonstrate that capillary fragility is an important factor in the premature infant and that the administration of vitamin K does not materially affect the hemorrhage after it has already begun. It was also found that the percentage of hemorrhagic manifestations was no greater in the premature infant, 9%, than in the full term infant, 6%.

There were no deaths from hemorrhage in the group not given vitamin K and one death from hemorrhage (cerebral) in the group given vitamin K. I have never thought that cerebral hemorrhage was influenced by the speed of blood coagulation. This study shows that even when vitamin K is given in ample amounts, cerebral hemorrhage occurs just the same.

Dr. J. H. Root, Jr., Waterbury, Conn.: Do you have any statistics on mothers who were given vitamin K?

Chairman Sanford: None of the mothers of the premature infants born in the hospital were given vitamin K. Almost all the mothers of those born at home received vitamin K before delivery.

Dr. Snelling: What about the prenatal diet of those in the home who later come to the hospital?

Chairman Sanford: It was not as adequate as those delivered in the hospital. The question was asked "Do I give vitamin K in hemorrhagic disease?" I have not given premature infants any vitamin K routinely in 10 years. I do give vitamin K in hemorrhagic disease if the condition is due to hypoprothrombenemia.

As to the administration of minerals, the only one you need consider is iron. We estimated the red cells and hemoglobin over a period of 5 years on 500 premature infants and found exactly the same results as were found by Blackfan several years ago, namely, that the premature infant, irrespective of birth weight, suffers a reduction of hemoglobin until about 10 weeks of age. There was then a static state for several weeks followed by a slow increase. The fall in hemoglobin does not depend upon the weight of the child but on the age of the child in weeks. A large premature infant leaves the hospital before this decrease is observed, whereas a small premature infant will stay in the hospital for weeks and become anemic because you are observing it at the time maximum decrease occurs. There are many clinics that give an iron preparation after the second week of life. We estimate the child's hemoglobin and erythrocytes beginning at the third week of life and if the decrease is below 10 gm. of hemoglobin, we administer iron. If it falls below 9 gm. of hemoglobin, we give a transfusion and then iron. I would say that about 50% will need iron therapy. Someone asked me about vitamin B_{12}. When the soluble preparation became available, we began to use it. All I can say is that thus far we have not observed any hematonic effect.

Dr. J. E. Brown, Columbus: How well do the premature infants assimilate the iron in the first few weeks?

Chairman Sanford: I think they assimilate it well. The preparation we use is U.S.P. iron and ammonium citrate, 50% solution. You can add 1 or 2 drops to each feeding.

Estrogen therapy was recommended by Shelton and Varden in 1946. They gave 2.5 mg. of methyl testosterone in the feedings. They later increased this to 5 mg. Confirmatory articles appeared saying that the resulting gain in weight shortened the hospital stay 50%. We used testosterone for a year with absolutely no effect. A recent study by Seitchek and Agesty on 57 premature infants reported no evidence of superior gain in weight.

Asphyxia is one of the most important things we have to contend with. Formerly there was no means of attacking this except clearing the child's air passages and giving unlimited oxygen. We found that the infant bronchosope, as used by House and Owen, is of great value in atelectasis if confined to 1 or 2 lobes.

If atelectasis is due to cohesion of moist surfaces of the lung sacs and you drain out a main bronchi you can eliminate cohesion in a single lobe. We now routinely take x-rays of all premature infants' chests if there is asphyxia as soon after birth as possible.

Dr. John J. Slavens, Toronto: I am very much interested to find out if you have ever discovered any relationship between asphyxia and the type of anesthesia used on the mother, intensity and the degree of anesthesia used at the time of delivery. Also, I would like to know if you have any cerebral trauma in the asphyxia.

Chairman Sanford: Yes, in the 2 deaths from cerebral hemorrhage quoted, there was asphyxia in both, which I think was more the cause of death than cerebral hemorrhage. The longer and heavier the anesthesia, the more the asphyxia.

Dr. Frank van Schoick, Jackson, Mich.: I have had some interesting experiences that might shed some light on these processes of resuscitation. For the past 18 years I have attempted resuscitation under direct visual control with the Flagg laryngoscope and a rubber-tipped tracheal insufflation tube which is long enough to reach the primary bronchi. There are 3 or 4 things I should like to mention. One, inasmuch as the fetus has respiratory movements in utero, the question is not "why does not the child breathe?" but why does it stop? This may be a little less true of the premature than the full term baby. Two, the larynx of the new born apneic baby is so poorly differentiated and possibly edematous that it looks very much like the external genitalia of the newborn female. When the insufflation tube is introduced into the larynx, occasionally gentle force must be used to get by the vocal cords. This force is not traumatizing as judged by the fact that I have never had a show of blood following the procedure. I question the possibility of passing a soft tracheal catheter by the usual digital methods in such a case. Three, with the insufflation tube in place and following the first good inspiratory effort, thin fluid comes cascading out of the larynx in a volume sufficient to soil the operator's gown. Four, on more than one occasion, with a tracheal tube in place, and after removing any mucus and fluid, CO_2, O_2 in a 5-95 mixture failed to establish respiration. When a

mixture of 30-70 was subsequently used, prompt and vigorous respiratory effort took place. To re-establish the normal respiratory mechanism after it has been depressed from any cause may require more than casual stimulation.

Chairman Sanford: At the present time we give as few fluids as possible except by mouth as plain water. In case of vomiting or diarrhea, fluids are given as conditions demand. After Branning's report in 1942 that the carbon dioxide content of the blood of the premature infant was less than that of the normal infant and that the blood organic acid content of the plasma was 2 or 3 times the amount considered normal for infancy, sodium lactate was given almost routinely to premature infants. Gamble in 1948 questioned whether an attempt to correct this acidosis was rational. A situation that is pathologic for older babies may be physiologic for the premature infant.

Clement Smith found in 1948 that disappearance of edema was accomplished by the loss of Na and K in the urine. Physiologically and clinically, therefore, it would not be indicated to flood the premature organism with fluids and minerals.

In regard to weight gain in premature infants, in a 5 year study of 500 the following was observed: We know that a full term baby can lose between 5 and 10% of its birth weight. The premature infant of 5 pounds will lose 12% of its birth weight and take 2 weeks to regain it. The premature infant that weighs 4½ pounds will lose about 15% of its birth weight and will regain it in 2 weeks. It will take another 2 weeks to gain to 5½ pounds, or about a month before the baby is ready for discharge. A premature that weighs 3½ pounds will lose almost 20% of its birth weight. It will continue to lose for about 2 weeks and will return to birth weight in 4 weeks. It will take 2 months before it will weigh 5½ pounds. With smaller prematures the loss will be 25% of their birth weight, or more than a pound. It takes a good month or more to regain this and they will remain in the hospital for 3 months before they are ready for discharge. The idea of getting them out of the hospital as soon as possible is laudable but it is important to remember that the average premature infant gains slowly and it should remain in the hospital until it can carry on its own existence.

Congenital defects represent 10% of premature mortality. The only one we wish to discuss today is retrolental fibroplasia. This was first described by Terry in 1942 as a congenital persistence of the primary vitreous. Owen later described instances where it developed after birth as an increased dilatation of the vessels. Krause believes that these 2 forms of disease are different. The first type, or congenital, is more often associated with cerebral and somatic defects. The second consists of eye defects alone. The increase in incidence varies in different parts of the country and even in the same city. Krause in Chicago reports 6.8% in 1937 and 30.4% in 1948. Our incidence is 6% and has remained unchanged throughout the years.

All agree that 75% are under 1600 gm. in weight. The increase is not due to saving more small premature infants for the proportion is the same over the past 10 years. Other causes given have been increased bleeding in the mother, fetal anoxia, virus disease and toxic agents. Ingals was unable to find any correlation from the mother's prenatal history. Vitamin deficiency has been thought to be a cause. Vitamin A has not decreased the incidence and vitamin E is not conclusive. Krause believes it may be the emulsifying agent used in water soluble vitamins. Incubator lights, drugs, iron and oxygen have all been considered as a cause. None have been proved.

The only difference in care that might account for the lower incidence in our premature group (6%) and others is that we give breast milk as a feeding. Whether this contains some protective substance we do not know.

Infections are difficult to diagnose in the premature infant as there are no characteristic physical signs. In 25 infants with various infections there was no one definite diagnostic point except jaundice which occurred in half of them. The same was true of laboratory tests. There was no characteristic finding except half the above infants showed anemia and a white cell count of over 12,000. It is best to remember that if the premature infant fails to gain, vomits or has any diarrhea, it may have an infection. Our treatment is to give such an infant pure breast milk and 100,000 units of crysticillin and streptomycin 0.1 gm./kg. until a definite organism is found. Then the antibiotics may be changed to suit the individual organism.

Premature mortality, as reported from various clinics in the country, varies from 12.7% to 22%. The mortality of premature infants born outside a hospital is from 10% to 15% higher than those born inside a hospital. Until uniform standards of prematurity are prevalent, it is useless to make any comparisons of mortality.

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE first communication is on "Health Insurance in Canada from the Paediatric View" by Dr. John Keith with an introductory letter from Dr. Alan Brown. In 1943, the Canadian Medical Association approved the principle of health insurance and set forth the opinion that health insurance programs should be developed by the various provinces in accordance with their local needs (J. Pediat. 31:228, Aug., 1947). In the intervening years some provinces have developed quite comprehensive programs of medical care (PEDIATRICS 7:430, 1951) whereas other provinces have taken very little action. The present communication describes these endeavors from the viewpoint of the pediatrician.

The second communication from Dr. John T. Fulton, Dental Services Adviser of the U. S. Children's Bureau, describes his observations of New Zealand's National Dental Service. The medical care program in New Zealand has received wide publicity; the National Dental Service, which was inaugurated much earlier, has received relatively little comment until recently.

The dental care problem everywhere is enormous. Children of school age average to develop one new caries lesion per year. The dental manpower currently available in this country does not begin to be adequate to deal with the problem; the result is that the majority of children enter adult life with a large accumulation of dental defects. The problem was particularly acute in New Zealand, which has one of the highest caries attack rates in the world and a limited supply of dental manpower. The School Dental Nurse is their attempt to solve this problem.

DEAR DR. HARPER:

Some time ago you asked me to write a comment on Health Insurance in Canada especially related to pediatrics, and I informed you that one of my colleagues, Dr. John Keith of the Hospital for Sick Children, was best fitted to state the situation.

To my mind he has expressed himself very clearly and outlined the conditions as they exist today in a much better manner than I would be to able to accomplish it.

There are two important points however that I should like to emphasize; first, that any pediatrician can practice successfully outside these organizations, and secondly, that an older pediatrician, say from 50 to 70 years of age, after he has established a reputation can do consultation and office practice with success, and charge the fees he thinks his services are worth. I might emphasize a third point, and say that the various voluntary insurance schemes are extremely helpful to the younger man starting up in practice.

ALAN BROWN, M.D.
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HEALTH INSURANCE IN CANADA FROM THE PAEDIATRIC VIEW

Before World War II there were less than 50,000 Canadians on any form of Health Insurance. There are now over 1,000,000 enrolled on Medical Insurance schemes sponsored by Medical Societies, as well as 2,750,000 (20% of population) on Blue Cross Hospitalization Insurance. As in other countries there have been pressures from many sides contributing to this movement. The depression of the early '30's played an important part. The Insurance principle is widely accepted, Hospital Insurance plans have been eminently successful, Group Insurance in companies is common. The men in the services liked the provision of medical care. The experiments in other countries, particularly in England, have been freely discussed in Canada. The Government because of this general interest began to prepare a bill formulating plans for Health Insurance.

The Canadian Medical profession at first reluctantly, and later more firmly, applied themselves to the job of meeting the challenge of this movement. They were consulted by the government and fortunately the government officials listened. As a result there has been no hasty legislation that has divided the country into rival camps. Rather than that, under the pressure of general interest, the medical profession have organized their own societies across the country and are learning to handle medical insurance both from the organizational point of view and also from practising it.

In 1951 there are now at least 30 such plans sponsored by the Medical Societies and local Medical groups in operation in the 10 provinces in Canada. During 1945 to 1950 a great deal of irritation was expressed by a large percentage of the contracting doctors who were taking part in these schemes. Now in 1951 there are many who still have objections to these schemes but the majority of the doctors in general practise are beginning to be conscious that the growing pains are lessening and to some degree the plans are workable. Paediatricians perhaps more than most groups have felt the growing pains keenly; this is partly due to the fact that all these medical insurance schemes were organized for operation with the general practitioner. Specialists other than paediatrics have fared better. For example, a surgical fee schedule has been drawn up that is sufficiently high enough to satisfy most general practitioners and most surgeons.

Health Insurance for Paediatric care is a part of the plan for all ages. This puts paediatricians in a minority group immediately. There is a further segregation in that paediatricians are found almost entirely in cities. This makes Paediatric Health Insurance a specialized problem. Wherever health insurance schemes have been in operation there are found to be three peaks in the cost per patient; in infancy, maternity, and in old age. Thus the paediatrician is usually paid a larger amount per patient than any other group of doctors on the scheme.

In Ontario where half the paediatricians reside the medical profession have arranged a Health Insurance scheme known as Physicians' Services Incorporated. Paediatric care is

encouraged by allowing five well baby visits the first year and three the second year. Under this the paediatrician is paid $3 for office visits, $4 for house calls. Since most paediatricians are now charging $4 and $6, the extra billing of the patient is necessary to make up the difference. This produces several problems. (1) The patient may not have been informed of this extra charge and the effect may be irritating. (2) It entails extra bookkeeping on the part of the doctor which costs him more in time and help. (3) The patient may not inform the paediatrician he is on this Insurance scheme when the doctor calls at his home. Later this comes up when the bill is sent. By that time the details of diagnosis are forgotten and poses a problem. (4) The Physicians' Services Incorporated pay only 90% of any doctor's claim. This 90% will vary depending on the prosperity of the times. The problem of bookkeeping is intensified for the paediatrician because his turnover of patients is so much greater than for most doctors in practise.

None of these problems are insurmountable but are indicative of the adjustment difficulties during this experimental period. Fortunately such schemes allow us to do our own experimenting on a small scale. One of the advantages the paediatrician has over the general practitioner in this P.S.I. scheme is that he is categorized as a specialist and thus allowed to charge extra if he considers his services warrant it. The general practitioner must only charge the fee laid down for general practitioners in the schedule of fees.

Plans vary in different parts of Canada. The scale of fees paid in British Columbia scheme is higher than that paid in the eastern provinces. Across the country the Health Insurance schemes pay $3 to $10 for a house call, and $2 to $5 for an office visit. The higher fees are paid in British Columbia where the paediatrician is paid as a specialist.

In two provinces only has well baby care been provided for. In Manitoba and Ontario, Manitoba allows payment on 7 office visits in the first year and 2 in the second; in Ontario 5 office visits are allowed in the first year and 3 in the second.

Most schemes pay 70 to 90% of the doctor's accounts based on the approved schedule, withholding the rest either because the scheme cannot afford any more on the premium paid, or to offset administration costs and to build up a reserve.

In the province of Quebec, Blue Shield Type of Insurance has been favoured and there are few subscribers on schemes which provide paediatric care.

As mentioned before the compelling force that has led to overcoming many of the difficulties and irritations that have arisen is the fact that by and large the mass of the population in Canada want some form of Health Insurance. If the medical profession had not energetically applied themselves to this problem and aided in establishing numerous schemes throughout the country, undoubtedly the government would have been forced to step in earlier. As it is, it seems likely that there will be a government-sponsored measure dealing with Health Insurance in the next few years, and the position of the doctor will be much more favorable if he has had considerable experience in operating such schemes and can prove he is able to administer a Health Insurance scheme efficiently on a good business basis.

Many of the paediatricians are finding the adjustment to medical schemes difficult and at times discouraging; in spite of that the majority are making an effort to make them workable. Those that are not cooperating in Ontario are still paid under the scheme by a settlement between the patient and the P.S.I. This is done because it is the policy of the P.S.I. to allow a free choice of doctor, so all doctors are paid whether they officially participate in the scheme or not.

Dr. John McCreary, who is chairman of the committee on Health Insurance in the

Canadian Paediatric Society, summed up the problem as follows: "It would seem that the entire question of whether we are satisfied to accept the additional bother which Health Insurance brings to our offices must depend on our view of the future of medical practise. If we honestly believe that there is no chance of any state medical scheme being put into effect, we are wasting our time with this relatively cumbersome method. If we do believe that there is a chance of this happening we are simply carrying out our share of the responsibility levied on all the medical profession to do what we can to have the system in effect which the government cannot afford to overlook in setting up its own routine. As has been discovered by every medical insurance scheme that has been tried in Ontario, the paediatrician takes more than his share of the total monies collected from the subscribers. Under these circumstances if the paediatrician withdrew from Health Insurance I am sure it would cause no great heartbreak in the various organizations. However if we feel the need to control our own future, I think we should do our utmost to work with these plans."

The paediatrician in Canada has three alternatives.

1. He may refuse to have anything to do with Health Insurance in medicine and adopt an essentially negative attitude.

2. He may make every effort to cooperate with the schemes being organized, particularly those sponsored by the medical profession.

3. He may adopt a middle of the road attitude by favouring Blue Shield type Insurance only. He would then carry on his own office practice with a minimum of contract obligation to the Insurance schemes. He would still have some patients who were paying into such schemes who would pose some problem to him. But looking into the future, he would be encouraging any government scheme to set up a plan which excludes the bulk of paediatric care.

The mode of approach of government, medical profession and laity in Canada has been a good one. There has been initiative on all sides and much experimentation. No one has been forced into a rigid mold as yet, everyone has developed a much clearer idea of what Health Insurance means but as yet the best way of applying it in Canada has not been agreed upon.

There is a general feeling however that the best in paediatrics should be incorporated in Health Insurance plans.

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NEW ZEALAND'S SCHOOL DENTAL NURSES

Through the auspices of the World Health Organization, I was able to observe New Zealand's National Dental Service at first-hand for 10 weeks during 1950. At that time their school dental nurse experiment in the dental care of children was entering its 29th consecutive year.

Essentially, the program is this: The New Zealand Department of Health (through its Dental Division, one of seven major divisions of the Health Department) carefully selects young women (high school graduates) every year. They are trained for two years and then assigned to school dental clinics throughout the country.

The New Zealand school dental nurse is a full time employee of the Health Depart-

ment from the moment she enters training. She receives no diploma or license and is required to spend her entire professional career in Government service.

These young women, working under the supervision of Health Department dental officers, perform all needed fillings, extractions, prophylaxis, topical applications of fluoride, simple gum treatments, and dental health education for elementary school children and any preschool child that applies for care.

Every New Zealand child between the ages of 3 and 13 is eligible for this dental service at no cost to him. The program, however, is not compulsory. The caseload is kept roughly at 500 children per dental nurse. Each child on the clinic rolls is examined twice a year and all necessary treatment is completed.

New Zealand operated 508 treatment centers in 1949, giving dental care to 235,746 children. This represents 73% of all New Zealand children between the ages of 3 and 13 years. The dental program serviced 2,333 (97%) of the primary schools, including the private and Maori (native) schools, and covered every section of the country, rural as well as urban.

In the past, New Zealand's dental nurse plan has excited little notice outside of its own country. Lately, however, the world-wide interest in the expansion of dental care for children, combined with the evidence of the wide disparity that exists between dental needs and dental services for children, has focused attention on New Zealand's program. Three independent studies were made of it in 1950.

The detailed report of my study has recently been published as a monograph by the World Health Organization.[1] The other two reports are also available—one by Dr. Allan Gruebbel of the American Dental Association,[2] and one by the United Kingdom Dental Mission.[3] In addition, I have made two supplemental reports which have been published in American journals; one on dental caries,[4] and the other on dental care.[5]

A discussion of my New Zealand material will follow four definite lines considered important by public health dentistry in the United States. These are: (1) Extent of the problem; (2) Methods of meeting the needs; (3) Resources to apply these methods; (4) Evaluation.

1. Extent of the Problem: Objective data on dental caries attack can be collected by a standard method. This method, called DMF, consists of counting the teeth decayed and untreated (D), those missing, or still present but beyond repair and, therefore, indicated for extraction (M), and those treated by a filling (F). The sum of these items is the number of permanent teeth ever attacked, or total dental caries experience (DMF).[6] The DMF method does not measure the extent of malocclusion nor the condition of the supporting tissues of the mouth. No objective yardstick for these conditions is available. Since caries is the most prevalent dental disease of children and the DMF index has been well tested for validity and widely used, it seems a fair measure of a dental problem.

The main part of my New Zealand study consisted of examining the mouths of school children, aged 7 to 14 years, and recording their dental caries experience in decayed, missing and filled (DMF) components. In all, the teeth of 4,072 children, equitably divided as to age, sex, and rural or urban residence, were examined. A summary of the data is given in table 1.

This table shows the high prevalence of dental caries. The average 7 year old has 2 permanent teeth showing evidence of caries attack and the average 14 year old has 10 such teeth. More than 5 of the primary molars have been attacked by age 7. Over the

TABLE 1

AVERAGE NUMBER OF ATTACKED TEETH PER CHILD, WITH 4-WAY BREAKDOWN OF "DMF" AND 2-WAY BREAKDOWN OF "d-e-f"; 4,072 NEW ZEALAND SCHOOL CHILDREN—1950

Capital letters refer to permanent teeth: "D" means carious, "X" means needing extraction, "O" means missing and "F" means filled. In respect to deciduous teeth, "d-e-f" means number of attacked molars, and "f" means number that were filled

	Age at Last Birthday								
	7	8	9	10	11	12	13	14	
2,048 Rural Children:									
DMF	2.16	3.27	3.94	4.55	5.75	7.17	8.77	9.85	DMF
D	0.34	0.30	0.35	0.44	0.49	0.73	1.00	0.98	D
X	0.00	0.00	0.01	0.02	0.00	0.02	0.07	0.04	X
O	0.00	0.03	0.03	0.03	0.04	0.11	0.18	0.22	O
F	1.83	2.94	3.56	4.06	5.22	6.30	7.52	8.61	F
def	5.44	5.28	4.71	3.56	1.77	0.61	0.19	0.07	def
f	5.20	5.00	4.55	3.39	1.60	0.52	0.14	0.07	f
2,024 Urban Children:									
DMF	1.86	2.90	3.70	4.29	5.50	6.98	8.98	10.13	DMF
D	0.68	0.47	0.36	0.59	0.53	0.66	0.99	0.99	D
X	0.00	0.00	0.00	0.02	0.04	0.04	0.11	0.12	X
O	0.01	0.03	0.02	0.04	0.08	0.08	0.37	0.42	O
F	1.17	2.39	3.31	3.64	4.85	6.20	7.51	8.59	F
def	5.34	5.33	4.88	3.43	1.82	0.57	0.29	0.15	def
f	5.01	5.02	4.57	3.20	1.65	0.54	0.20	0.11	f
2,040 Boys:									
DMF	1.77	2.92	3.65	4.24	5.34	6.71	8.32	9.48	DMF
D	0.54	0.39	0.33	0.44	0.46	0.61	1.00	0.99	D
X	0.00	0.00	0.00	0.02	0.02	0.03	0.08	0.07	X
O	0.00	0.01	0.01	0.02	0.06	0.06	0.23	0.27	O
F	1.23	2.52	3.31	3.76	4.80	6.00	6.99	8.14	F
def	5.24	5.22	5.01	4.02	2.11	0.70	0.32	0.14	def
f	4.85	4.88	4.80	3.75	1.92	0.64	0.21	0.12	f
2,032 Girls:									
DMF	2.24	3.24	3.97	4.62	5.88	7.48	9.48	10.54	DMF
D	0.48	0.38	0.38	0.58	0.55	0.79	0.98	0.98	D
X	0.00	0.00	0.01	0.02	0.03	0.04	0.10	0.10	X
O	0.00	0.05	0.03	0.05	0.06	0.13	0.30	0.39	O
F	1.76	2.81	3.55	3.97	5.24	6.53	8.10	9.06	F
def	5.58	5.39	4.60	2.97	1.50	0.47	0.14	0.08	def
f	5.35	5.14	4.35	2.84	1.35	0.41	0.13	0.06	f
All 4,072 Children:									
DMF	2.01	3.09	3.82	4.44	5.62	7.08	8.87	10.01	DMF
D	0.51	0.38	0.36	0.51	0.51	0.70	0.99	.99	D
X	0.00	0.01	0.01	0.02	0.02	0.03	0.09	.08	X
O	0.00	0.02	0.02	0.03	0.06	0.10	0.27	.33	O
F	1.50	2.67	3.44	3.87	5.03	6.25	7.53	8.60	F
def	5.42	5.31	4.80	3.50	1.80	0.59	0.24	0.11	def
f	5.11	5.01	4.57	3.30	1.63	0.53	0.17	0.09	f
Age	7	8	9	10	11	12	13	14	

8 year age span the incidence rate is one new attacked permanent tooth each year. This indicates that, in New Zealand, dental caries in children is a health problem of the first magnitude.

The data for attacked permanent teeth displayed in table 1 are typical. Nearly all published DMF figures follow this pattern—rising steadily as age advances, with an increment of about one new attacked tooth per year. In comparing these findings with data collected by the same method in several areas of the United States, New Zealand ranked third.[4] Five of the areas had an attack rate of 7 or more for children aged 12 to 14 years.

2. Methods of Meeting the Needs: Fundamentally, dental public health uses two methods to meet a dental caries problem of this size: (a) Measures to prevent the attack of the initial caries lesion and (b) repair of the annual increment of lesions that cannot be prevented.

a. Preventive measures—up until the advent of fluorides—were limited to oral hygiene, adequate diets and the reduction of fermentable carbohydrate intake. All of these methods require personal application. The dentists advise and recommend, but the child must apply them himself. Parents and children must cooperate. To promote this, dental health education has been the first plank in the dental public health platform.

From the beginning, the New Zealand dental nurse was expected to be a health educator. Teaching method and materials have always been a part of her training. One of her regular duties is to give a prescribed number of hours to health education each month. Also, as a member of the staff of the school where the clinic is located, she takes part in the school's health education program.

In addition, the Division of Dental Hygiene has an extensive program of health education, using movies, slides, exhibits, posters, leaflets, demonstrations and the like. Included in this program are periodic messages in the public transportation advertising spaces and the showing, twice a year, of dental health movies in every picture house in the country. In the light of this organized effort—and remembering that dental nurses operated in 97% of the elementary schools—it is probable that dental health education is more widespread and systematic in New Zealand than in any other country in the world.

The topical applications of sodium fluoride to the teeth of children had been done experimentally in the clinic of the Training School for Dental Nurses for about a year, as of April 1950. A recent communication from New Zealand states that this preventive measure is now being added to the routine procedure of all school dental clinics.

So far as I could gather, the fluoridation of domestic water supplies was not being considered in New Zealand in 1950. Available reports indicated that the waters were fluoride free.

b. The repair of the annual increments of carious lesions that appear in the teeth requires regular and systematic examination and treatment. Since caries attack the teeth of young children, it is important that systematic care begin early.

The New Zealand system is geared strictly to this base. Beginning children are preferred at the age of 3 years but first enrollments are permitted through the primer age (5 to 6 years old). Beyond that age a child is not enrolled in a clinic unless the mouth is first put in order by a dentist at the parent's expense. This rule also applies to the reinstatement of children who have failed to attend the clinics regularly.

Normally, a child is given systematic dental care through the entire elementary school period. But of late years, due to the heavy postwar birth rate, clinic enrollments have been

flooded with primer-age children. At the same time, high school graduating classes have been smaller—a reflection of the low birth rate of the early '30's. Since fewer girls are graduating, there are fewer candidates for dental nursing. As a result, adequate staffing of school dental clinics has been a difficult problem. In this situation, however, rather than sacrifice complete and systematic treatment in order to spread the service more widely, older children have been removed from the rolls. In 1950, many school clinics had discontinued service for children beyond the age of 11.

3. Resources to Apply These Methods: The way in which New Zealand has marshalled its resources is the most interesting and certainly the most controversial part of its dental program. Only in the last 10 years have most countries given serious thought to the quantity and distribution of dental manpower. New Zealand felt this need three decades ago. There were not enough, nor did it seem that there could be enough, dentists trained to provide systematic care for all of its children. Evident, too, in its dental literature of that period, is the belief that dentists were too highly trained to be satisfied with the routine work of a school dental clinic. Also few of them would be satisfied in rural areas.

At all events, the decision was made to train and employ auxiliary personnel. The dental profession was not unanimous in this decision, by any means. Although officially approved in principle by the Dental Association, the idea of a young woman, with only two years of training, performing operative dentistry for children was widely criticized. In fact, the matter was in controversy for some time. By and large, the dentists now consider the school dental nurse an essential and effective member of the public health system of New Zealand.

4. Evaluation: The New Zealand program, in common with dental programs everywhere, has had little success in preventing dental caries. A group of 14 year old children, averaging 10 permanent teeth showing evidence of carries attack, would seem to indicate this.

Nor is this lack of success surprising in the light of the methods available. There is scant evidence to show that tooth brushing will prevent dental caries to an appreciable extent. This method, to be effective at all, must be done immediately after eating, a requirement that is hard to gear into the average child's schedule.

Evidence is also thin that optimum diets influence caries attack rates. Interestingly enough, many New Zealand dentists are beginning to question the long-standing practice of furnishing free milk to school children. They feel that milk is contributing to increased dental caries.

There is much evidence that fermenting carbohydrates in the mouth will initiate carious lesions. Conversely, there are strong data to support the preventive aspects of limiting such food in a child's diet. Little can be hoped for, however, from this method on any public health scale. New Zealand, like the United States, is in the top bracket of per capital sugar consumption.

The fluorides, then, are the most effective preventives now available to dentistry. Topical applications of fluoride should show their benefits quickly in New Zealand, as that country has a made-to-order organization for giving this treatment to every child in a short time.

In evaluating dental care in New Zealand, the DMF data are of further value. Two aspects of dental caries experience appear in these findings: first, the large proportion of filled teeth found in both the permanent and primary dentitions—since filled teeth reflect how closely dental needs are being met; and, second, the low rate of tooth mortality, or

missing permanent teeth—since this percentage shows the terminal result of failure to control dental caries.

Tooth mortality rates are probably the most objective long-term index of the effectiveness of a caries control program. Basically, the purpose of dental care is to preserve and stabilize the functional occlusion of the teeth. Uncontrolled dental caries eventually ends in tooth loss. Every tooth loss is a loss of function. Carious teeth cannot repair themselves. Early replacement of carious lesions by fillings, however, does preserve the teeth for long periods. This fact is reflected in collections of data showing the percentages which the missing (M) and filled (F) components of total DMF comprise. Where a given level of care has existed for several years, the M component is high if the F component has been low; or, if the F component has been high, the M component is low. The New Zealand data in table 1 are arresting in this regard. Tooth mortality (X plus 0) is almost nil through the age of 11 and filled teeth comprise 90% of the caries attack rate. Even at age 14, when most of the children have been away from the school clinics for two years, filled teeth represent 86% of the attack rate and tooth mortality averages less than one-half tooth per child. These rates reflect the regular and systematic care for children in New Zealand.

In the 1946 study of child health services, made by the American Academy of Pediatrics, figures are available for dental clinic services in the United States. The data from this study on the total number of services per child, the hours of service per child, and the ratio of fillings to extractions indicate further the relationship between the amount of dental service given to children and tooth mortality. The less service for each child, the more need for extractions.[5]

Thus, in New Zealand, despite a persistent dental problem, a high proportion of attacked teeth have been treated in the form of fillings and a low tooth mortality rate has been achieved. To this extent New Zealand's school dental nurse program has been successful.

There are other advantages, too. The program has made it possible to bring systematic dental care to all children, even to those in remote rural areas where dentists could not, or would not, practice. Furthermore, dental care is a regular part of school life, dispensed and accepted on the same basis as the three "R's." The children appear to regard the dental nurse in the same light as the teacher. For this reason the dental clinic, like the classroom, has possibilities far beyond its standard purpose. Predicated upon her insight and enthusiasm, the school dental nurse can be a counselor, guide and friend—a steadying influence during that time when mental hygiene is the most promising and effective.

Then, there is the matter of cost. Adequate financing of dental programs is always difficult because of the universal need. The dental nurse system has made possible a nationwide service at a reasonable public health cost. Figures furnished by the Division of Dental Hygiene in New Zealand indicated that the over-all expense of the program was £1 8/11—which at the 1950 exchange rate was about $5 per child, per year.

Since a dental degree now requires six years of study in most countries of the world, the question arises whether a two year course can equip a person to adequately diagnose and treat a child's dental ills. The New Zealand dental nurse's work is restricted to the services listed earlier. She does not diagnose nor give treatment for malocclusions, pulp involvement, fractured teeth, mouth infection, or oral surgery, other than the simple extractions. She is trained to screen such conditions and to refer them to dentists for treatment. The records disclose that about 4% of the children seen in the clinic in 1949 were

referred in this manner. This figure did not include referral for orthodontic care, since such treatment is not paid for under the program.

It should be remembered that when children are brought under dental care at an early age and given systematic examination and treatment, extractions are greatly reduced, as are related conditions such as deep cavities, pulp exposures, abscesses and general oral sepsis. Usually, in dental clinics for children, the demands for service far exceed the available dentist-hours. Service must be spread so thinly that complete treatment at any time is difficult. In fact, very few clinics are able to keep up to date with new increments of need by regular, periodic care.[7]

Dental needs, accumulating in this fashion, go from bad to worse. By the time the child finally gets treatment the problem is extensive and serious. In a dental care program, such as is maintained in New Zealand, the majority of dental needs are simple ones since dental caries is treated before the teeth get in serious condition.

Another question is the complete divorcement of this program from dental education in New Zealand. Since school dental nurses are providing the bulk of dental service for young children, it seems unfortunate that they are not tied in more closely with the overall dentistry of the country. In the beginning, it was felt undesirable that the nurses should acquire any great knowledge of general dentistry. After years of operation, however, with the program being accepted as necessary and desirable, it would seem advantageous for dentists and dental nurses to understand more of each other's aims and contributions. At least some interchange of faculty between the University Dental School and the Training School for Dental Nurses seems called for. Since 1947, the practicing dentists of New Zealand have been closely related to the National Dental Service by working under contract on an agreed fee basis for children up to the age of 16 who no longer are eligible in the school dental clinics. In 1949, some 73% of the practicing dentists in New Zealand were operating in this program. This would make it seem doubly important that the training of dentists and dental nurses should dove-tail.

The need for this "Adolescent" service furnished by the dentists points up the fact that dental care for children, no matter how regular and systematic, cannot be discontinued at 13 years of age. Dental caries is very active in adolescence and without continuing treatment much of the good work accomplished in early childhood can be undone. Much evidence has accumulated in recent years to this effect. New Zealand's experience supports it.

Prevention of dental disease remains a serious and acute public health problem in New Zealand. In common with the world at large, New Zealand has used little of its funds for dental research. Their resources, compared with those of some of the larger countries, are quite limited. It may be, also, that the success of the program of treating caries of children has over-shadowed the needs for preventive measures. On the other hand, New Zealand has been quick to put into practice the research technics developed in other countries.

It can be argued, perhaps, that a sounder dental health program would be developed by concentrating on preventive research rather than treatment. So far, however, no measure (even the fluorides) prevents dental caries altogether. For example, the most valuable of all the teeth for long-term dental health are the first permanent molars. At the same time they are the most highly susceptible to caries attack of all the teeth. They continue to be attacked in spite of preventive measures. They will continue to be lost prematurely unless they are given regular attention. Furthermore, fluorides do not arrest a caries process that has already begun. Therefore, maximum results of preventive measures will not be

achieved for a considerable period of time. It is practically certain that every country will continue to face substantial correction problems in the future.

New Zealand has demonstrated that a program of training dental nurses is one effective solution of those problems: Nearly all of the children of New Zealand are under systematic dental care, which, at least for a very substantial proportion of them, would not otherwise be available. Certainly, this is a real contribution to the development of public health dentistry.

But, could the school dental nurse system be considered a model? Is it appropriate for other countries? Is it the only possible solution of the dental manpower problem?

There are no pat answers. The problems of providing dental care to children vary from one country to another and, in this country, from one State to another. There are marked differences in dental caries attack rates, numbers of children under care, numbers and distribution of dentists, and financial resources. It is in the light of such problems that school dental nurses will have to be considered.

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TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE CLARK REPORT ON HEALTH INSURANCE PLANS

AN OBJECTIVE and factual study of existing health insurance plans, authorized somewhat over a year ago by the Senate, has been released by the Senate Labor and Public Welfare Committee.* The report was prepared by a special staff working under the direction of Dr. Dean A. Clark, Director of the Massachusetts General Hospital. In submitting the report to the Senate, Senator Lehman (N.Y.) stated:

"Your Subcommittee on Health regards it as the most complete, unbiased, and definitive compilation of data on the subject currently available anywhere. We believe it represents an outstanding contribution to our knowledge of the problems of health insurance. We think it will prove of great value to doctors and laymen concerned with the extension and expansion of health insurance programs and to legislators concerned with the many-sided problem of how the people of America can best finance their participation in our American system of medical care.

"Nevertheless, the Subcommittee on Health wants it clearly understood that the report does not set forth any recommendations for legislation directly affecting the economics of medical care and that it represents the findings of Dr. Clark and his associates rather than the opinion of the subcommittee or any of its members."

SUMMARY OF FINDINGS

Number of People Enrolled

One half of the 150 million people in the United States have insurance against some part of the costs of medical care and half have not been reached by voluntary medical-care insurance.†

In the half of the population with some form of medical-care insurance, 23 million persons (15 percent of the total population) have only hospital insurance; an additional 31 million people (21 percent of the population) have some degree of protection against the costs of both hospital and surgical care; another 17 million people (11 percent of the population) have hospital, surgical and limited medical insurance, including specified benefits for the costs of physicians' services in the hospital for non-surgical cases, and limited home or office care in some plans. Between 3 and 4 million people (less than 3 percent of the population) have comprehensive medical-care insurance, including physicians' care by both specialists and general physicians in the home, office, clinic and hospital, preventive as well as curative services, bedside nursing in the home, X-rays, laboratory and other diagnostic tests, ambulance service, and other auxiliary benefits. No two plans are exactly alike, but practically all of the people with comprehensive medical-care insurance also have hospital insurance and the two together represent comprehensive medical-care coverage.

* Health Insurance Plans in the United States, Report of the Committee on Labor and Public Welfare, United States Senate, Washington, D.C., Government Printing Office, 1951.

† Estimated as of the end of 1950.

The "Haves" and the "Have-nots"

Certain factors are noted among people who have some form of medical-care insurance in comparison with those who have not.

In general, voluntary medical-care insurance is most common among people easily accessible to group insurance and less common among those difficult to reach by the group method. There is far greater concentration of the "haves" in industrial, urban areas than in rural areas. The proportion of persons having hospital insurance is twice as high in urban as in rural states. Income per capita also appears to have an influence. Twice as many people (per unit of population) have hospital insurance in states with high per capita incomes as in states with low per capita incomes.

Although it is generally agreed that families at lower-income levels have greater needs for medical care than higher-income families, nevertheless the self-supporting families of the lower income levels are to be found among the "have-nots" in much greater proportion to their numbers than families of middle or somewhat above middle income. Except through those plans which provide group insurance and in which the employer bears at least half the cost, it is difficult to reach these lower-income families.

Also among the "have nots" are two groups of the population with rather special needs for medical care: newborn infants during the first weeks of life and persons over 65 years of age. For the most part, newborn infants are included only in the comprehensive plans and in about one-third of the Blue Cross plans. Persons in the older age group have less medical-care insurance in proportion to their numbers than younger people. Some plans have age limits for new subscribers or disqualify subscribers over certain ages when they change from group to individual status.

Negroes have relatively less medical-care insurance than white people, particularly in the southern states where the Negro population is most concentrated. This may be due to such factors as the following: relatively fewer available medical personnel and facilities, economic status, education levels and other problems.

Others for whom voluntary medical-care insurance is relatively difficult to provide include self-employed persons, farmers, and individuals in small establishments to whom group insurance of any kind cannot be easily applied. They can, it is true, buy individual insurance if they can qualify for it and if they can afford the cost which is greater than group insurance.

The Proportion of Medical Care Costs Covered by Insurance

The total expenditures for medical care in the United States in 1949 are estimated to have been from 10 to 11 billion dollars, of which 9 to 10 billion were for medical care and 1 billion for public health, research and education. Of the 9 to 10 billion dollar medical care bill, medical-care insurance paid about 8 percent (755 million dollars). Individual private payments accounted for about 70 percent, another 20 percent was paid from local, state and federal tax funds (not including the Armed Forces) and less than 2 percent was contributed by charitable gifts, income from hospital endowments and the like.

There are differences of opinion as to what portion of the costs of medical care should be considered insurable and as to what groups of the population can or should be enrolled. If we assume that all of the costs of physicians' and general hospital services now supported by private expenditures may be insured through voluntary plans, the $755 million paid in benefits by all forms of medical-care insurance in 1949 constituted about 17

percent of the approximately $4.4 billion in private expenditures for these purposes. If we assume that insurance is practicable for all private expenditures for the services of physicians, hospitals, dentists and nurses, and for one-third of the expenditures for drugs and medical supplies, including the net cost of insurance—$6.4 billion in 1949—the amount now insured is about 12 percent. If we assume that only five-sixths of the private expenditures for the services of physicians and general hospitals may or should be insured, the percentage insured in 1949 was about 21 percent. Conversely, by the highest of the above estimates, voluntary insurance plans do not cover about 80 percent of that portion of the Nation's medical-care bill generally regarded as the minimum that is potentially insurable.

Insurance Benefits for Hospital Care and Physicians' Services

The largest part of the amount paid out in medical-care insurance benefits is for hospital care. Of the total $755 million, insurance benefits for hospitals amounted to $530 million in 1949, while benefits for physicians' services totaled $225 million. Less than $1 million was attributable to other services such as dental care, nursing, drugs or medical supplies outside the hospital.

If the benefits are related separately to the total private expenditures for general hospital care and to the total private expenditures for physicians' services, a further interesting comparison is noted. Insurance benefits paid about one-fourth of the $2,027 million expended for general hospital care and one-tenth of the $2,267 million expended for physicians' services. Although the total bill for physicians' services is somewhat larger than that for hospital care, the latter is the most widely insured item. Expenditures for dental care, nursing care, one-third of the costs of drugs and medical supplies outside the hospital together with the net costs of insurance amounted to approximately $2,056 million in 1949. Insurance benefits for such items were negligible.

Existing Voluntary Insurance Programs

At present there are three large groups of organizations which provide medical-care insurance: (a) the nonprofit Blue Cross-Blue Shield plans; (b) the casualty, life and other insurance companies; (c) a number of organizations independent of the first two groups, including industrial and labor union plans, consumer cooperatives, programs under the auspices of private medical groups, some medical societies, community organizations and others.

As noted above, about half of the total population, 75 million persons, had at the end of 1950 some form of hospital insurance either alone or in combination with surgical or surgical and medical insurance. About half of the 75 million were insured through Blue Cross plans. Forty-eight million persons (who are also included in the 75 million) had insurance against some of the costs of physicians' services, mostly surgery and non-surgical physicians' services in the hopital. Of this 48 million about 18 million were enrolled in the nonprofit Blue Shield and similar plans and about 30 million people held insurance company policies.

Concluding Findings of Report

The bulk of existing medical-care insurance is for hospital care, surgery and in-hospital physicians' services. It does not attempt to cover, for the most part, protracted illness (hospitalized or nonhospitalized) such as chronic disease, nor does it meet the medical

expense of preventive care and physicians' care for short-term nonhospitalized illnesses, or for illnesses in their early stages. This emphasis upon hospitalization, surgery, and in-hospital physicians' services furnishes an incentive to physicians and patients alike to increase to an extent greater than medically necessary the performance of surgical procedures or the use of hospital-bed facilities, and, therefore, the need for hospital construction. It also does little to encourage preventive medicine, early diagnosis or treatment. A different pattern is set by those comprehensive plans that stress preventive medicine and the provision of services outside of the hospital.

It is self-evident that the mechanism of insurance substitutes a recurring periodic charge for medical bills of uncertain amounts, that insurance of even limited scope tends to reduce—in differing degrees—the burden of large medical bills, but that under the present pattern of medical-care insurance there remains an additional financial problem for those with insurance who have a serious illness requiring nursing services, expensive diagnostic services and a protracted period of hospitalization.

Measures to improve the kind and quality of medical services have been included in very few voluntary insurance plans, except those providing comprehensive services through medical group practice units. The growth of comprehensive insurance has been restricted by difficulties of initial financing and organization, by the frequent opposition of organized medicine, and by restrictive laws enacted in more than half of the states, usually at the instance of physicians and medical societies.

NEWS AND ANNOUNCEMENTS

Sir James Spence, M.D., Director of the Department of Paediatrics and Nuffield Professor of Child Health, King's College, Newcastle-upon-Tyne, England, will deliver the twentieth annual series of the Benjamin Knox Rachford Lectureships on Thursday evening, Nov. 1, and Friday evening, Nov. 2, 1951, at 8:30 p.m. in the auditorium of the Children's Hospital Clinic and Research Building, Cincinnati. The titles of his lectures are (1) "The Experience of the Universities in Medical Education" and (2) "The Experience of Paediatrics in the Universities."

* * *

Dr. Martha M. Eliot has been nominated as the fourth Chief of the United States Children's Bureau. She joined the Children's Bureau staff in 1924 and was appointed Assistant Chief of the Bureau in 1934 and made Associate Chief in 1941. For the past 2 years, Dr. Eliot has been serving as an Assistant Director General of the World Health Organization.

* * *

Dr. Thomas E. Shaffer, formerly with the Departments of Pediatrics and Preventive Medicine at Ohio State University, Columbus, Ohio, has been appointed Professor of Preventive Pediatrics at Temple University School of Medicine and Coordinator of Community Activities for St. Christopher's Hospital for Children, Philadelphia.

* * *

The University of Minnesota announces a Symposium on Rheumatic Fever to be presented Nov. 29 and 30 and Dec. 1, 1951. The Symposium is being given with the sponsorship and financial support of the Minnesota Heart Association. All interested physicians, teachers and investigators are cordially invited to attend. There will be no tuition nor registration fee.

* * *

A Postgraduate Course in Pediatric Allergy will be given at New York Medical College, Flower and Fifth Avenue Hospitals, Nov. 7, 1951, through May 28, 1952—30 Sessions Wednesdays, 9:00 A.M. to 4:00 P.M. Fee $300.00.

This course consists of lecture-seminars, laboratory, clinical procedures, clinic work, ward rounds and animal experimentations. Lecture-seminars cover the basic principles, diagnosis and treatment of allergy in children and applied immunology.

Applicants must be certified in pediatrics or have the requirements for certification. Applications to be made to the:

Dean, New York Medical College
106th Street and Fifth Avenue
New York 29, N.Y.

* * *

Announcement is made of Research Fellowships in Pediatric Allergy in the Departments of Pediatrics and Immunology, New York Medical College, 106th Street and Fifth Avenue, New York 29, N. Y.

These Fellowships are full time. One starts July 1, 1951, the other January 1, 1952. Applicants must be certified in pediatrics or have the requirements for certification. The Fellowships run from 1 to 2 years and will consist of intensive training in immunology and animal research pertaining to the field of hypersensitiveness; intensive study of allergic children, which will include skin testing, laboratory work, clinical follow-up, as well as clinical research. Applicants who have had previous training in chemistry and/or immunology and who are desirous of a research career will have preference.

* * *

PROCEEDINGS OF THE ATLANTIC CITY SESSION OF THE AMA

Awards: Medal awards were made to exhibits for original investigation and for teaching value. The Gold Medal was presented to Willis J. Potts, William L. Riker and Robert DeBord, Children's Memorial Hospital, Chicago, for the exhibit on Surgery for Congenital Heart Disease. The Certifi-

cate of Merit award was presented to Benjamin M. Gasul, Egbert H. Fell, Maurice Lev, William P. Mavrelis, Oldrich Prec and Raul Casas, Hektoen Institute of Medical Research, Cook County Children's Hospital, Presbyterian Hospital, and the University of Illinois College of Medicine, Chicago, for the exhibit on Congenital Heart Disease in Pediatrics—a Study of Over 700 Cases.

Section on Pediatrics: The following were elected officers of the Section on Pediatrics: Chairman, Dr. Walter B. Stewart, Atlantic City; Vice Chairman, Dr. Eugene T. McEnery, Chicago; Secretary, Dr. Wyman C. C. Cole, Detroit; Delegate, Dr. Woodruff L. Crawford, Rockford, Ill.; Alternate Delegate, Dr. Oliver L. Stringfield, Stamford, Conn.; Alternate delegate to fill unexpired term of Dr. Julius Hess, now delegate because of resignation of Dr. William Weston, Sr., Dr. Woodruff L. Crawford, Rockford, Ill.; Custodian of the Abraham Jacobi Fund, Dr. Hugh L. Dwyer, Kansas City, Mo.; Representative to Scientific Exhibit, Dr. F. Thomas Mitchell, Memphis, Tenn.

ERRATUM

On page 153, first line of text under notice of M & R Pediatric Research Conferences, July issue of PEDIATRICS, vol. 8, 1951, the firm name of McKesson and Robbins Laboratories was used instead of M & R Laboratories.

CORRESPONDENCE

EDITOR OF PEDIATRICS
DEAR DOCTOR:

The furor created by the reports of paralysis occurring in extremities injected with antigens in patients developing poliomyelitis within one month after the injection has assumed the proportions of hysteria.

Anderson and Skaar (PEDIATRICS 7:741, 1951) clearly acquit "injections" given prior to one month before the onset of poliomyelitis of any recognizable part therein and certainly play no part in the etiology of poliomyelitis itself.

The public and many public health authorities however are reacting to the serious detriment of the overall disease prevention picture.

Fortunately large epidemics of poliomyelitis are relatively infrequent. They do strike terror in parents' minds and hearts when they occur. These epidemics are less devastating than would result if immunization programs were interfered with as a result of the hysteria now rampant.

One is impressed by the paucity of cases even in epidemics of recently immunized children having paralysis in extremities in which injections have been made. Even in the epidemic of poliomyelitis discussed by Anderson and Skaar the number "pointing to possible causal relationship" boiled down to 33 children out of 2790 cases and this in a community having at least an estimated two thousand children given antigens as of even date.

Incidentally, Martin (Arch. Dis. Child. **50**:1, 1950) includes an injection of penicillin in his group. How many children received penicillin in Minneapolis during the epidemic months is beyond conjecture and how many were subsequent poliomyelitis victims was not touched upon in Anderson and Skaar's very excellent presentation.

It has been repeatedly noted over the past fifty years that violent exercise, hard work or particular stress will be followed by localization or increased paralysis in that part bearing the brunt of effort. It is sincerely hoped that a restatement of this axiomatic truth does not induce guardians of our health, both elected and self constituted, to close our recreational facilities, our factories, stop our building of homes and let our farms lie fallow for each summer season.

The many non-epidemic years are being overlooked in this reckoning. In Philadelphia in 1950, 150 proved cases were reported to the Department of Public Health. Of these four had received antigens. All four received "cold vaccines" and alum-precipitated toxoid, two cases three days prior to symptoms of poliomyelitis, one case three weeks prior and one case four weeks prior to the onset of poliomyelitis. In none did paralysis develop in the arm injected. May this not be typical of most communities most of the time? The odds against an immunized child are really infinitesimal.

The other side of the picture is worthy of note. Only one generation of babies not immunized against diphtheria would put us back to the days of over five thousand cases of diphtheria with five hundred deaths annually in a community of a million population.

Stop smallpox vaccination and smallpox would become a pediatric problem again instead of an almost historic disease in enlightened communities.

Pertussis and tetanus immunizations are really still in their swaddling clothes but they are well proving their efficacy.

Had the pioneers in diphtheria prevention been thwarted because of hysteria when the four deaths from an improperly made toxin-antitoxin mixture occurred in Dallas about 1920 diphtheria prevention would have died aborning.

In the early days of smallpox vaccination tetanus occurred from time to time. Was that a propitious time to stop vaccination? It was not stopped.

Out of the recent past men of fortitude fought prejudice, had the courage to face obstacles and learn from experience how to meet lay temerity. Pediatrists and public health officers should show the same magnificent quality of leadership today to preserve the ground won and prepare for further advances.

What is needed now is a universal method of application of our immunization procedures. Since

there are multiple advantageous immunizations and perhaps new ones available at any time it means concentration upon refinements of procedure, materials and technique to perfect these agencies and simplify their use.

Patience is needed because there are more programs of immunizations in practice than are justified. This is the subject for study and being guided by hasty hysterical conclusions or judgments is not the way to do it. The effect of immunization on an occasional poliomyelitis victim unhappy as it may be should not vitiate the over-all program of prevention of more serious communal disasters such as diphtheria, smallpox, pertussis epidemics or stop the mastery of tetanus.

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Philadelphia

Editor's Comment: The above letter was submitted to Dr. John J. Miller, Chairman, Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases, for an opinion. He has replied that "In the forthcoming revision of the Report of the Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases, the following statements on this subject will appear:

Under the heading of "Contraindications to Active Immunization Procedures" appears:

"The existence of poliomyelitis in epidemic proportions in the community should be a signal for the reconsideration of injections and vaccination. If diphtheria, pertussis and smallpox are not prevalent, and if the infant's parents rely closely on pediatric supervision, delay is warranted. The committee makes this as a temporary recommendation until the reported association between parenteral injections of various agents (including penicillin) and poliomyelitis is clarified."

Under the heading of "Poliomyelitis, Care of Exposed Susceptibles" appears:

"Careful observation of contacts should be carried out through the period of isolation. During this time it is wise for sibling and other contacts to avoid over-exertion, chilling, fatigue and such other things as may be expected to reduce general resistance. Furthermore, contacts should not be subjected to subcutaneous or intramuscular injections of immunizing agents or hormones when these may readily be deferred for a few weeks. Should contacts require penicillin, the oral route should be elected unless circumstances dictate otherwise."

BOOK REVIEWS

SOME SPECIAL PROBLEMS OF CHILDREN AGE 2 TO 5 YEARS, Nina Ridenour, Ph.D., and Isabel Johnson, Philadelphia, National Mental Health Foundation, Inc., 1949, 25 cents, 72 pp.

This small pamphlet is packed full of sound principles about child development and behavior, and gives many clues to the better management of the so-called behavior problems that beset parents, teachers and pediatricians so overwhelmingly today. Although it was written for parents and teachers primarily, this material may serve the pediatrician as well, as a primer on child psychology. The authors present their material briefly, in simple English with apt illustrations. The construction of the paragraphs facilitates further ease of reading and grasp of information. Topics discussed include what to do when a child hurts other children, when he is destructive, uses bad language, as well as the other worrisome and parental bogies as thumbsucking, enuresis, masturbation and fears. This pamphlet is strongly endorsed and recommended for every pediatrician as early in his career as possible both as a practitioner of medicine and as a parent. It is hoped that through the pediatrician these pamphlets will become available to their patients.

Single copies may be obtained from the National Mental Health Foundation, 1520 Race St., Philadelphia. There are special quantity-purchase rates.

MENTAL HYGIENE IN PUBLIC HEALTH, Paul V. Lenkau, M.D., New York, McGraw-Hill, 1949, $4.50, 396 pp.

The author is a psychiatrist at Johns Hopkins University who has pioneered in the field of mental hygiene and psychiatry as it might be applied in public health. The author described methods of integrating principles of mental hygiene with public health practice and uses his own vast experience in this area to illustrate in a practical fashion how such a synthesis may be brought about. The book will be of interest to pediatricians whether or not they work in the field of public health specifically, inasmuch as modern pediatric care includes preventive medicine. There are 2 parts to this book; in the first, the author defines mental hygiene and relates it to the field of public health; in the second part, the development of the personality is delineated beginning with the prenatal period on through senility and old age. Pediatricians will find in the sections on the prenatal, natal, infancy, preschool and school periods much that will explain the psychology of the child as he relates himself to other persons. The emphasis throughout is on prophylaxis, although an appendix describes the pathology and symptoms of some of the common mental diseases. Throughout the book there are many excellent references on behavior and growth and development, and the appendix contains references on visual aids which teachers will find helpful in discussing the age periods described in detail throughout the major portion of the book.